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INTERNAL MEDICINE

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Paul J. Rosch

Acute Tubular Necrosis
L. W. Bluemle Jr., G. D. Webster Jr., and J. R. Elkinton

Deaths from Bites and Stings of Venomous Animals and Insects in the United States
Henry M. Parrish

Single-Disk Antibiotic-Sensitivity Testing of Staphylococci
Alfred W. Bauer, David M. Perry, and William M. M. Kirby

Acute Dissecting Aneurysm of the Aorta
Julian R. Beckwith, William H. Muller, W. Dean Warren, and J. Edwin Wood Jr.

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Serotonin and the 5-Hydroxyindole Pathway of Tryptophan Metabolism
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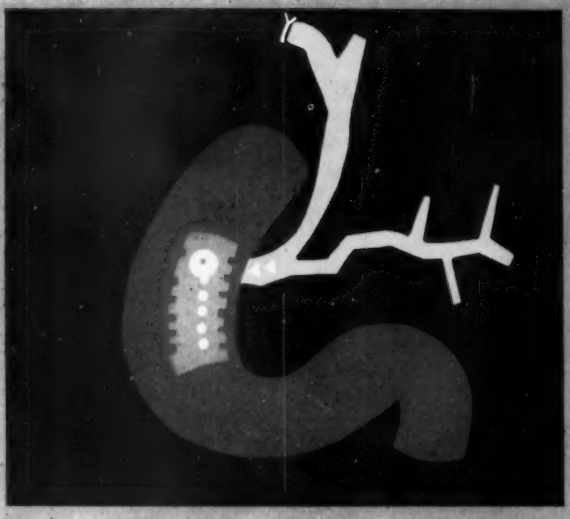

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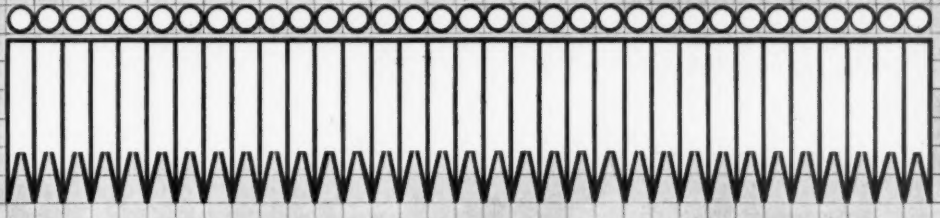

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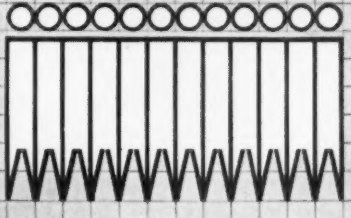

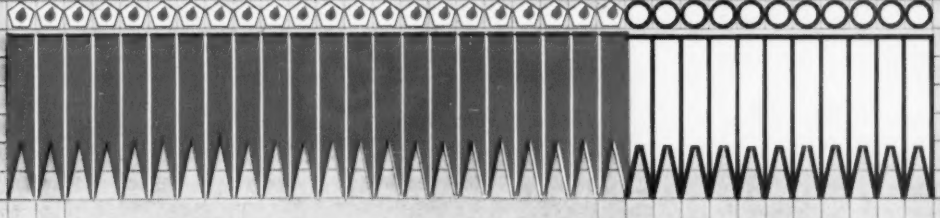

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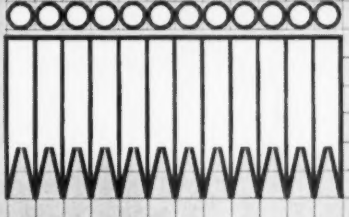

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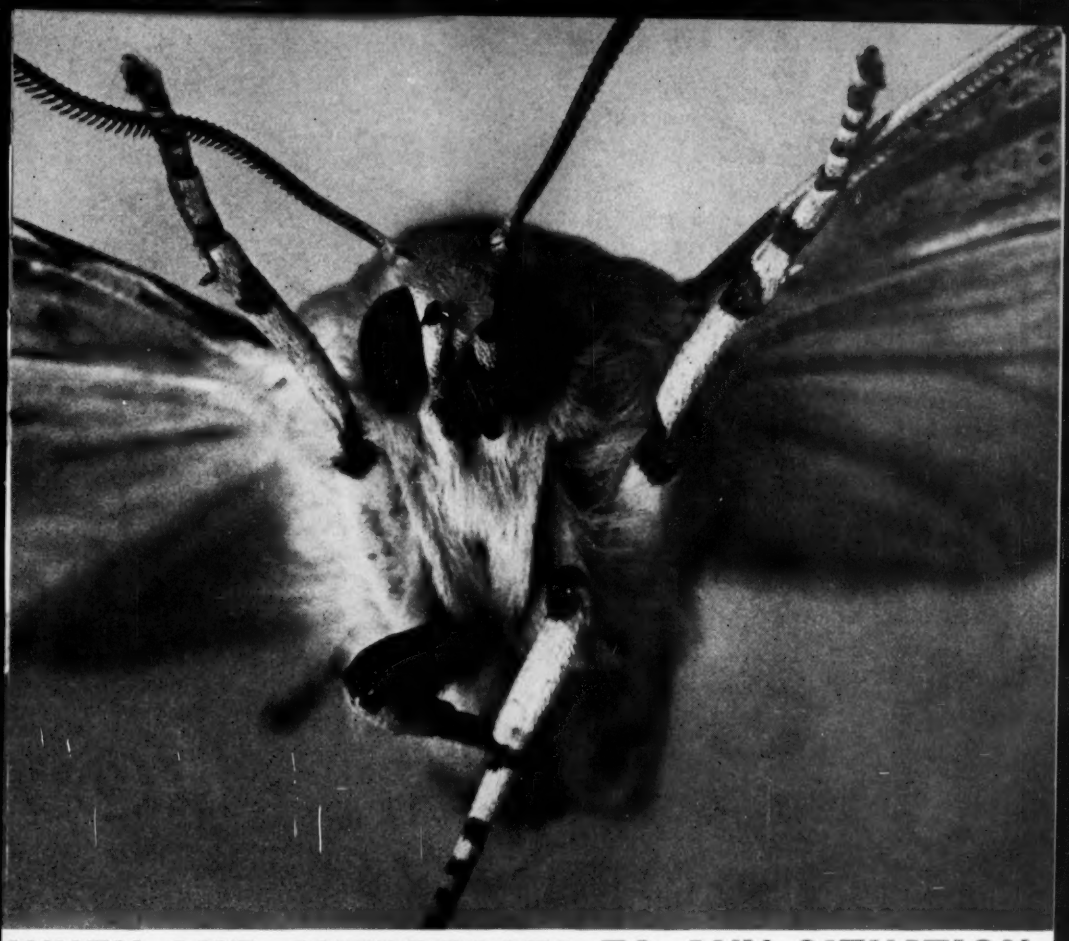

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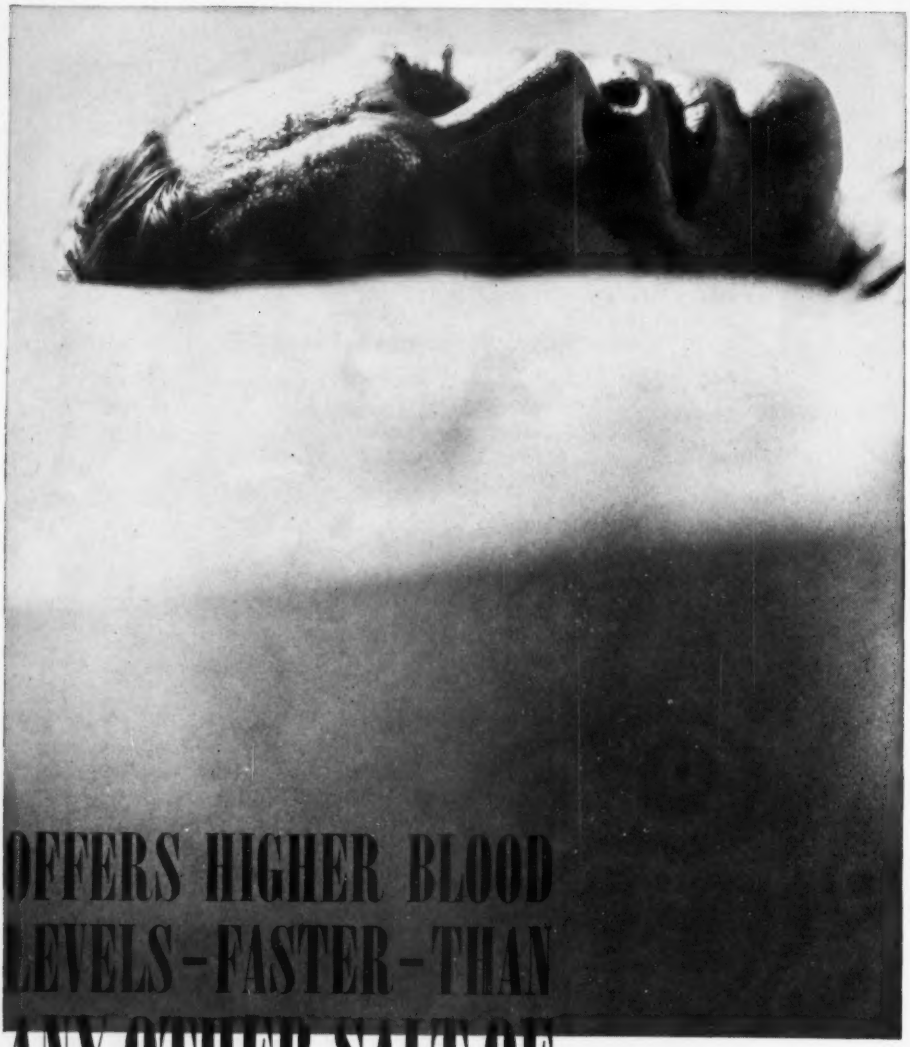

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INTERNAL MEDICINE

Editorials

Gastrointestinal Bleeding in Pheochromocytoma and Following the Administration of Norepinephrine (Arterenol)

Gastrointestinal symptoms have always been recognized as a prominent manifestation of pheochromocytoma. The first successful removal of a pheochromocytoma [1] was occasioned by complaints of abdominal pain and vomiting, and the first correct diagnosis and cure reported [2] occurred in a patient with recurrent attacks that could apparently be terminated only by nausea and vomiting. The initial description of the syndrome of paroxysmal episodes [3] was of a 28-year-old woman with "troubles nerveux caracterises par des crises paroxystiques de constriction épigastrique, de nausées et de vomissements," and, in what was probably the first case reported,[4] over 70 years ago, vomiting was a significant feature. In recent years, while attention has been focused on the cardiovascular and metabolic manifestations of pheochromocytoma, gastrointestinal symptoms have been noted to occur in over one-third of one series,[5] with abdominal pain being frequently mentioned as a significant feature or presenting complaint.[5-9]

In view of the above background, it is somewhat surprising that relatively little recognition has been given to gastrointestinal bleeding in this condition. Indeed, a recent extremely comprehensive review of obscure causes of gastrointestinal bleeding [10] failed to include pheochromocytoma in the differential diagnosis, although even a casual experience with the literature reveals repeated instances in which this proved to be a significant feature of the patient's clinical course.[6,9,11-15] It is not unusual to read of patients with pheochromocytoma who are diagnosed or treated as chronic duodenal ulcer [6,7,12,16]; yet, although even an association with gallstones has been suggested,[17] little comment has been directed to lesions in the small bowel. A possible direct relationship between gastrointestinal bleeding and pheochromocytoma has been recognized by some investigators,[9,14,15] while others have described petechiae or changes in the blood vessels in various portions of the gastrointestinal tract without further comment.[5,13,18-20]

A review of the available material strongly suggests that gastrointestinal bleeding in pheochromocytoma is not related to blood pressure elevation per se. The lesions seen are not particularly common in other forms of severe hypertension and are demonstrable in cases of pheochromocytoma in which an elevated blood pressure has been a relatively minor or late consequence. One reported case

Submitted for publication Sept. 16, 1958.

describes recurrent exsanguinating hemorrhages over a three-year period necessitating two negative exploratory operations, in which significant hypertension was only a late feature.[14] Autopsy examination in this case revealed no gross pathology in the gastrointestinal tract. The significance of this complication is further attested to by other experience. The 8-year-old patient of Cone, with a norepinephrine (arterenol)-secreting tumor, died because of perforation of the ileum and subsequent peritonitis. Microscopic evidence of an occlusive endarteritis with infarction was noted.[15] Changes such as these do not appear to be a result of an elevated blood pressure alone. Talbot presents a case in which marked necrotizing obliterative endarteritis and ulceration of the mucosa of the ileum were seen,[5] and a review of 17 autopsied cases of pheochromocytoma under age 55, at the Armed Forces Institute of Pathology, reveals 2 instances in which perforation of the ileum led to the patient's death.

Current studies suggest that there may be a direct relationship between catecholamine excretion and such hemorrhagic lesions in the intestinal tract as well as in the heart [21-23] and liver.[24] Szakacs has shown that in dogs the infusion of norepinephrine in amounts comparable to those used in certain clinical situations will result in reproducible areas of submucosal hemorrhage associated with periarterial inflammatory changes in various portions of the small intestine.[22,25] This is not too surprising, since experiments performed almost 20 years ago with intraperitoneal epinephrine and norepinephrine would produce similar changes in guinea pigs, dogs, cats, and rabbits,[26] and epinephrine has been used since 1903 to cause experimental degenerative lesions in large vessels,[27,28] although necrosis in the dog ileum has also been seen.[29] In clinical practice, tissue necrosis due to norepinephrine is not limited to the site of intravenous infusion,[30,31] and it has been suggested that remote areas of vasoconstriction and necrosis might be expected to occur, particularly in regions where the blood flow has been previously compromised by prolonged hypotension,[32] as in the intestine. Support for this comes from recent observations at the Armed Forces Institute of Pathology, which suggest that vascular damage and hemorrhage in the intestine may be a consequence of the prior administration of norepinephrine to patients in shock.[33]

This perhaps offers an alternate explanation for the changes described in a recent article, entitled "Infarction of the Bowel in Cardiac Failure," which postulates that severe cardiac failure and accompanying vascular spasm can result in infarction of the bowel.[34] In the two cases presented in which the pathology was said to be caused by cardiac failure alone it may be pertinent to note that both patients received levarterenol (*l*-norepinephrine). In addition, the pathology of the small bowel consisted of inflammatory changes in the submucosa and serosa, with cellular changes and hemorrhagic characteristics similar to those described above in the experimental animals. The mesenteric vessels showed no evidence of occlusion or narrowing. It seems very likely that the administration of norepinephrine may have had a significant role in the pathogenesis of such lesions, and it may be relevant that infarction of the bowel has increased appreciably in the present decade with the concomitant increased use of norepinephrine in cardiac failure. It is of interest that the patient with the most extensive changes, in this report, also received hydrocortisone, an agent known to potentiate the vascular damage produced by norepinephrine.[21,23] Similar pathology can be found in another report in which hypertension was not a significant factor but large amounts of norepinephrine were required.[31]

The frequency with which this phenomenon occurs clinically may depend upon a variety of factors governing local hemostasis, blood flow, pH[53], or possibly the release of serotonin. It may be pertinent to note that melena is frequent in the carcinoid syndrome, and hemorrhagic lesions in the intestine can be produced by serotonin administration.[36] Although it is conceivable that the adrenal cortex might participate in this, especially in view of increased activity and known synergism,[21,23] no additional agency need be invoked, in view of the well-established direct effects of epinephrine and norepinephrine on vasculature in the small intestine.[37,38] The irritable response to topically administered epinephrine seen in minute blood vessels in the rat mesoappendix has long been used as a criterion for measuring vasodepressor and vasoexcitor materials,[39-42] and norepinephrine is even more effective than epinephrine in causing constriction of the mesenteric bed *after intra-arterial injection.*[43] It is possible that certain gastrointestinal lesions seen during the "alarm reaction" [44] are mediated through systemic or local release of catecholamines or tryptamines alone,[45] perhaps potentiated by increased thyroid [27] or adrenal cortical activity.[46] It is also interesting to speculate on the possible mediation of peptic ulceration after intracranial operations,[47] especially those associated with stimulation or excitation along the course of the fiber tracts from the anterior hypothalamus to the dorsal motor nucleus of the vagus.[48] Hypothalamic activation has been shown to result in secretion of both epinephrine and norepinephrine,[49,50] and vagal stimulation can apparently produce subendocardial hemorrhages [51] similar to those produced by norepinephrine infusion experimentally.[21-23] The vagotropic action of norepinephrine and even epinephrine has been well documented.[52,53] Conversely, hypothalamic stimulation can be demonstrated after intravenous epinephrine,[54,55] and increased adrenal medullary activity during stress has been well appreciated since Cannon's experiments, so that ample experimental background exists to support the thesis that catecholamine excess may be a factor in so-called "stress ulcers" (air-raid ulcers).[44,56]

On the basis of the above observations, the indiscriminate use of norepinephrine as the agent of choice in combating hypotension, especially when associated with gastrointestinal bleeding or perforation,[57] appears unwarranted and potentially dangerous. This seems especially true in view of the common lack of restriction on the amount administered or the rate of infusion, since restoration of the blood pressure to normal is usually the only criterion that determines such factors. The common practice of adding hydrocortisone to increase the pressor effect [58] may increase the damaging response seen with norepinephrine at otherwise innocuous levels. In addition, it is suggested that gastrointestinal bleeding may be a significant and physiologically relevant observation in certain patients with catecholamine-producing tumors.

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Acute Tubular Necrosis

Analysis of One Hundred Cases With Respect to Mortality, Complications, and Treatment With and Without Dialysis

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In theory the mortality rate from acute tubular necrosis should be low. The reasons for this are several. First, the damaged renal tubule is able to undergo more or less complete regeneration. Second, physiologic principles have been applied to minimize the fluid and electrolyte alterations which accompany acute renal failure. Third, there has been almost universal acceptance of hemodialysis as a procedure capable of improving many of the biochemical abnormalities and the symptoms attributable to them. Thus, Strauss and Raisz state, "The mortality in acute tubular necrosis itself can be reduced by the combination of physiologic measures and external dialysis to nearly zero."[1] Some reports give the impression that this goal is being achieved.[2-5] Standing in contrast to this theory, however, are the discouraging results obtained at the renal centers with the most experience despite the best management currently available, including dialysis. Our mortality rate in 100 cases of acute tubular necrosis is 50%.

In an effort to refocus attention on the entire spectrum of this disease, we have undertaken this analysis of our cases with respect to the various factors which contribute to both morbidity and mortality. The results clearly indicate that the prognosis is related both to the nature of the injury leading to the renal damage and to the ensuing complications. An improved survival rate therefore will require further efforts directed toward the understanding and prevention of complications.

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Material

The disease under consideration is *acute tubular necrosis*.[6] It encompasses a variety of causes and degrees of parenchymatous damage[7] and is frequently difficult to differentiate clinically or even pathologically from other types of acute renal failure. Within these diagnostic limitations, however, the present series is composed of patients whose disease onset, course, or necropsy findings indicate that potentially reversible renal tubular necrosis was present. The criteria for inclusion of cases in this series agree in general with those of Swann and Merrill.[8] We have omitted cases in which it appeared that the onset of diuresis was secondary to the correction of hypotension, hyponatremia, or dehydration rather than to healing of the tubular lesion. We have omitted cases of acute glomerulonephritis and acute pyelonephritis. In contrast to Swann and Merrill, we have not excluded cases with preexistent renal disease if the clinicopathologic picture indicated that acute tubular necrosis was superimposed or cases in which oliguria lasted less than four days when the subsequent course or pathologic examination revealed distinct evidence of renal damage. We have also included two cases of bilateral cortical necrosis because recovery of adequate renal function has been documented in a number of patients with this disease.[9-12]

This series is composed of 100 patients under the care of one or all of us between 1949 and 1958 (Table 1). Twenty-two were initially inpatients at the Hospital of the University of Pennsylvania, and seventy-five were transferred from other hospitals between the 2d and 13th days of their disease (mean 6.8 days). The remaining three were seen and followed closely by one of us in nearby hospitals.

TABLE 1.—*Case Material*

Case	Sex	Age	Principal Cause	Contributing Factors	Length of Oliguria, Days	Day of Dialysis *	Result	Day of Death	Probable Cause of Death
1	M	65	Extravasation of urine following prostatectomy	Hypotension during surgery	9+		Died	10	Hemorrhage from eroded esophageal artery
2	F	40	Incompatible transfusion		13+		Died	14	Purulent tracheobronchitis
3	M	40	Incompatible transfusion	Laminectomy	13		Survived		
4	F	19	Fever of unknown origin		14		Died	28	Ventricular fibrillation
5	F	32	Septic abortion		10+		Died	10	Potassium intoxication
6	M	40	Incompatible transfusion	Splenectomy following traumatic rupture	12	12	Survived		
7	M	55	Hemolysis following transurethral resection		10+		Died	11	Congestive cardiac failure
8	M	29	Fever of unknown origin		4		Survived		
9	F	51	Bichloride of mercury ingestion		13		Survived		
10	F	24	Incompatible transfusion	Postpartum hypotension	10	9	Survived		
11	F	27	Bichloride of mercury ingestion		10		Died	82	Septicemia
12	M	54	Hypotension during cystectomy	Carcinoma of urinary bladder	8+	7	Died	9	Potassium intoxication
13	M	67	Hemolysis after transurethral resection		5		Survived		
14	F	44	Incompatible transfusion	Cholecystectomy	13	9	Survived		
15	F	40	Hypotension during mitral commissurotomy	Rheumatic heart disease	10+	6, 10	Died	10	Cardiac arrest
16	F	17	Incompatible transfusion	Mitral commissurotomy, congestive heart failure	9	6, 11	Survived		
17	F	57	Choledococystectomy, resection of duodenum		5		Died	15	Peritonitis, pneumonia
18	M	48	Crush syndrome	Toxin	10+	5, 9	Died	10	Diffuse hepatic necrosis
19	F	21	Septic abortion		9	7	Survived		
20	F	40	Incompatible transfusion	Panhysterectomy with excessive bleeding	12	8	Survived		
21	F	58	Shock following mitral commissurotomy	Congestive heart failure	9	8	Survived		
22	F	30	Shock following lobectomy	Pulmonary tuberculosis, amyloidosis of kidneys, adrenals	4+		Died	5	Adrenal insufficiency
23	F	60	Shock following facial resection		16	9	Survived		
24	M	34	Shock during adrenal exploration	Adrenocortical carcinoma, 2nd exploration because of bleeding	16	13, 19	Died	41	Pneumonia & peritonitis
25	M	65	Prostatectomy	Hypertension	4+		Died	5	Potassium intoxication
26	F	67	Common duct exploration		10	8	Died	17	Intraperitoneal hemorrhage
27	F	42	Incompatible transfusion	Panhysterectomy	10	8	Survived		
28	F	32	Bleeding following Caesarian section	2 laparotomies because of bleeding, infectious hepatitis	10	10	Survived		
29	M	37	Incompatible transfusion	Resection of duodenal adenoma	13+	6, 10	Died	14	Acute pancreatitis
30	F	43	Shock following hysterectomy		9+		Died	9	Potassium intoxication
31	F	36	Septic abortion	Postpartum hypotension	3		Survived		
32	M	22	Crush syndrome	Nephrectomy for lacerated kidney	9	9, 14	Died	24	Uremia †

TABLE 1.—*Case Material* (Continued)

Case	Sex	Age	Principal Cause	Contributing Factors	Length of Oliguria, Days	Day of Dialysis *	Result	Day of Death	Probable Cause of Death
33	F	76	Incompatible transfusion	Anemia	12		Survived		
34	F	55	Bichloride of mercury ingestion		8		Survived		
35	F	26	Incompatible transfusion	Abruptio placentae, shock	6		Survived		
36	M	58	Cardiac arrest	Previous renal disease, congestive heart failure	5		Died	35	Acute myocardial infarction
37	M	40	Klebsiella pneumoniae		7+	6	Died	8	Pneumonia
38	F	36	Incompatible transfusion	Abruptio placentae, Caesarian section	7	8	Survived		
39	F	59	Incompatible transfusion	Pyelonephritis, postnephrectomy hypertension	8		Died	21	Septicemia
40	F	28	Incompatible transfusion	Caesarian section	12	13	Survived		
41	F	24	Bichloride of mercury ingestion		4+		Died	5	Pneumonia
42	M	70	Shock following aortic graft		5+		Died	5	Intraperitoneal hemorrhage
43	M	55	Aortagram	Arteriosclerotic cardiovascular disease	12	13	Survived		
44	M	49	Incompatible transfusion	Gastrectomy	18+	14	Died	19	Pulmonary edema, bilateral renal cortical necrosis
45	F	28	Shock during laparotomy		20+	13	Died	21	Peritonitis and widespread colitis
46	M	19	Crush syndrome	Prolonged hypotension	12+	6, 10	Died	13	Acute respiratory failure
47	M	65	Shock following perineal resection	Hypertension, nephrosclerosis	10+	7	Died	11	Uremia †
48	M	40	Carbon tetrachloride		13	11	Survived		
49	M	64	Acute cholecystitis		16	11, 18	Died	18	Aspiration pneumonia
50	F	24	Abruptio placentae	Afibrinogenemia, preeclampsia	16	5, 11, 35	Died	48	Aspiration pneumonia
51	M	58	Extravasation of urine following prostatectomy	Hypertension, chronic pyelonephritis, laparotomy	11+	9	Died	11	Pulmonary edema
52	F	23	Incompatible transfusion	Caesarian section with hypotension	11		Survived		
53	F	37	Postpartum hemorrhage & shock	Afibrinogenemia	1		Survived		
54	F	20	Septic abortion		11		Survived		
55	M	28	Crush syndrome	Shock following surgery	6		Survived		
56	F	23	Shock following caudal anesthesia	Afibrinogenemia	10		Survived		
57	M	53	Extravasation of urine following suprapubic cystostomy		11+	10	Died	12	Acute respiratory failure
58	F	27	Septic abortion		12	7, 15	Died	36	Septicemia
59	F	40	Diarrhea of unknown etiology with shock		6	6	Survived		
60	F	32	Septic abortion		<4		Survived		
61	F	26	Postpartum hemorrhage & shock		4		Survived		
62	F	50	Incompatible transfusion	Whipple resection	9		Survived		
63	F	32	Incompatible transfusion	Incomplete abortion	18	13	Died	28	Septicemia
64	M	62	Shock following subtotal gastric resection	Hypertension, chronic pyelonephritis	9		Died	15	Acute respiratory failure
65	F	22	Abruptio placentae		14	10	Survived		
66	M	30	Crush syndrome		13	11	Died	19	Pulmonary edema

67	M	62	Pneumococcal pneumonia	Multiple myeloma	7		Survived		
68	M	64	Shock following nephrectomy	Chronic pyelonephritis	10+	10	Died	11	Septicemia
69	M	49	Shock following aortic valvulotomy	Chronic congestive heart failure	9	8	Died	13	Ventricular tachycardia, cardiac failure
70	M	68	Incompatible transfusion		15		Survived		
71	M	37	Unknown nephrotoxin	Toxic hepatitis	<4		Survived		
72	F	42	Carbon tetrachloride		7+		Died	8	Acute hepatic necrosis
73	M	64	Hemolysis following retropubic prostatectomy		8+		Died	9	Pneumonia
74	F	36	Incompatible transfusion	Incomplete abortion	11	13	Survived		
75	F	44	Septic abortion		3		Survived		
76	F	36	Acute cholecystitis		4		Survived		
77	M	58	Shock following aortic graft	Arteriosclerosis	9		Died	16	Multiple arterial & venous thromboses
78	F	24	Incompatible transfusion	Postpartum hemorrhage	11	8, 12	Survived		
79	M	54	Crush syndrome		6+		Died	6	Intracranial hemorrhage
80	M	44	Shock following cholecystectomy		7	7, 10	Survived		
81	M	46	Unknown	Dehydration	6		Survived		
82	M	44	Carbon tetrachloride		10+		Died	10	Acute hepatic necrosis
83	M	60	Prostatectomy		4		Survived		
84	F	33	Postpartum hemorrhage & shock	Afibrinogenemia	6+	4	Died	6	Convulsion with cardiac arrest
85	F	40	Shock following mitral commissurotomy		9		Survived		
86	F	23	Hemorrhagic meningoencephalitis	Dehydration	7		Died	16	Pneumonia
87	M	43	Incompatible transfusion	Shock following cholecystectomy	13+	10	Died	13	Hyperkalemia
88	F	43	Shock secondary to undiagnosed infection		9		Survived		
89	F	40	Incompatible transfusion	Postpartum hemorrhage, afibrinogenemia	12	11	Survived		
90	M	46	Incompatible transfusion	Cholecystectomy	17	7, 13	Died	17	Uremia †
91	M	44	Carbon tetrachloride		11+	4, 6	Died	11	Diffuse hepatic necrosis
92	F	77	Aortic graft	Chronic renal disease	12	13	Survived		
93	M	63	Rupture of spleen		5		Died	5	Intra-abdominal hemorrhage
94	F	30	Postpartum shock		9	5	Survived		
95	M	49	Shock following laparotomy	Renal infarct	8	7	Died	19	Pneumonia
96	M	46	Shock following laparotomy	Chronic pyelonephritis, peritonitis	4		Died	8	Peritonitis
97	M	62	Hemolysis following prostatectomy		15	8, 13	Survived		
98	F	28	Postpartum hemolysis	Chlostridial infection	17	7	Survived		
99	M	46	Shock from meningitis	Acute pyelonephritis	6		Died	20	Subarachnoid hemorrhage
100	M	65	Hemolysis following prostatectomy		11	8	Survived		

* Day after onset of oliguria.

† Uremia as a cause of death signifies that death could not be attributed to any single complication. These patients' terminal course was marked by coma, progressive acidosis, uremic frost, pericarditis, and generalized bleeding.

General principles of management of all patients during the oliguric period while under our care included limitation of fluid intake to approximately 600 ml. plus the sensible external loss,[28] very low or no intake of protein and potassium, and the administration of 100-350 gm. of carbohydrate daily, mostly as hypertonic glucose solutions. Steroid therapy has not been used except in exceptional circumstances when specifically indicated. In those cases where hemodialysis was performed, the Skeggs-Leonards, Engleberg and Inouye, or Kolff twin-coil apparatus was used. Other details of management have been discussed previously.[14,28] Oliguria is arbitrarily defined as a daily urine volume of less than 400 ml.

Over-All Mortality Rate

The total mortality rate was 50%. This figure agrees well with those reported by other authors who have treated a large number of these patients. Swann and Merrill, in their excellent review of 85 cases, reported a mortality rate of 48%.[8] Teschan and co-workers[16] observed a mortality of 53% in 51 wounded soldiers with acute renal failure treated during the latter part of the Korean War at the Renal Insufficiency Center, where an artificial kidney was available. Other series have reported mortality rates of 34%-50%.[17-21] A recent analysis of 791 cases, compiled from the statistics of nine independent renal centers, revealed an overall average of 43%.[22]

Some smaller series of patients have shown a lower mortality. In some, the difference can be explained in part by a predominance of patients whose renal failure developed as a complication of pregnancy, transfusion reaction, or exposure to toxic agents, all "low mortality" groups which will be discussed in the following section.[11,23-30] In other series, the mortality rate is lower because of the exclusion of patients dying of their initial illness or from some other nonrenal complication during recovery from renal failure.[3,31] Unfortunately, corrected statistics of this sort ignore the detrimental influence which uremia may exert on the patient's potential for recovery from any illness or complication. They further tend to give a false basis for evaluating prognosis in any given case.

TABLE 2.—*Size and Mortality Rate of Various Etiologic Groups*

Etiology	Total Cases, No.	Survived, No.	Died, No.	Mortality Rate, %
Surgical complication	32	9	23	72
Trauma	6	1	5	83
Transfusion hemolysis	24	17	7	29
Obstetrical complication	16	12	4	25
Nephrotoxin	9	4	5	55
Miscellaneous	13	7	6	46
Total	100	50	50	50

Relationship of Mortality Rate to Etiologic Background

Analysis of the cases according to the etiologic background reveals significant differences in mortality rates. The cases have been divided according to common factors in the development of the tubular necrosis, namely, (1) surgery, (2) trauma, (3) transfusion hemolysis, (4) obstetrical complications, (5) exposure to nephrotoxic agents, and (6) unknown or miscellaneous factors. This division in some cases has had to be arbitrary when several etiologic factors coexisted. All patients sustaining hemolytic transfusion reactions are included in this group (3) regardless of other possible classifications. Table 2 summarizes the sizes and mortality rates of these groups.

Surgical Complications.—In the majority of patients who developed oliguria after a surgical procedure there was a significant fall in blood pressure of varying duration but the oliguria continued after restoration of blood pressure to normal. In four patients there was no recorded fall in peripheral blood pressure; nevertheless, the pathogenesis of the renal failure was probably the same, namely, a marked reduction in renal blood flow without an accompanying peripheral vascular collapse.[32] In eight cases where prostatectomy was performed, the onset of oliguria was associated with intravascular hemolysis, which was attributable in four cases to the use of distilled water as an irrigating solution.

There are 32 cases in the surgical group. The mortality rate was 72%. Of the 23 fatalities, death in 11 was probably due to the basic disease process present before renal damage occurred, such as abdominal infection, congestive heart failure in patients undergoing cardiac surgery, adrenal insufficiency, separation of abdominal aortic grafts, and myocardial infarction, occurring after almost complete recovery from renal failure. The remainder died of complications arising after the onset of renal failure.

Trauma.—This group consists of six patients, five of whom died of their disease. Three patients suffered multiple and severe injuries in automobile accidents; one patient's pelvis was crushed in a construction accident; another patient sustained severe muscle destruction and gangrene of an arm while in an alcoholic coma, and one patient suffered multiple fractures and a cerebral laceration from a fall. The renal lesion was thought to be directly responsible for death in two patients. Death in the others appeared to result primarily from the initial injury.

Transfusion Hemolysis.—Definite evidence of transfusion hemolysis was taken to be (*a*) major incompatibility demonstrated by cross match, (*b*) evidence of hemoglobinemia and/or hemoglobinuria, and (*c*) an elevated or rising titer of specific red cell antibodies in the recipient's serum.

Twenty-four patients are included in this category, with a mortality rate of 29%. In six of the seven fatalities death did not appear to result directly from the preexisting disease which gave rise to the need for transfusion. There was no correlation between the amount of incompatible blood given and the severity of the renal damage. Oliguria lasted 15 days in one patient (Case 70) after only 60 ml. of incompatible blood was given preoperatively for correction of anemia. This patient recovered, as did a patient (Case 20) who received over a two-day period 2,000 ml. of blood incompatible by major cross match.

In 16 instances, including 5 of the fatal cases, the administration of incompatible blood resulted from a typing error, improper labeling, or mistaken identity of two patients with the same surname. At least four additional mishaps might have been avoided had Coombs' antiglobulin serum been employed routinely in cross matching.

Obstetrical Complications.—Sixteen patients developed acute renal failure as a result of obstetrical complications: three from placental abruption, six from postpartum hypotension, seven from septic abortion. There were four deaths in this group. One fatal case (Case 50) was found to have marked bilateral renal cortical necrosis at postmortem examination despite the fact that her 24-hour urine volume reached a peak of 2,000 ml. and azotemia was decreasing prior to death. Death in the remaining three resulted from sepsis (Case 58), potassium intoxication (Case 5), and sudden cardiac arrest (Case 84).

Nephrotoxins.—There were nine patients exposed to nephrotoxic substances. Carbon tetrachloride was responsible in four cases, bichloride of mercury in four, and an unknown substance in one case. The mortality rate in this group was 55%. In three of the five fatal cases death was attributable to the effects of the toxic agent on organs other than the kidney: One died of diffuse hepatic necrosis; one, of aspiration pneumonia secondary to vomiting soon after ingesting poison, and the third, of sepsis secondary to perforation of the gastrointestinal tract.

Miscellaneous Factors.—Thirteen patients are included in this category, either because of an uncommon etiologic background or because the responsible factors could not be determined. Renal failure occurred following an aortogram in one (Case 43), following a nontraumatic rupture of the spleen (Case 93), and during severe infections, such as pneumonia (Cases 37, 67, 99), cholecystitis (Cases 49, 76), fever of undetermined origin (Cases 4, 8, 88), diarrhea of unknown cause (Case 59), and dehydration (Cases 81, 85). The mortality rate in this group was 46%.

Comment.—Other authors have also noted that prognosis varies markedly with the na-

ture of the antecedent disease. Our mortality rates of 25%-29% in cases occurring as a result of transfusion reactions or obstetrical complications are in accord with other published reports.[24-29] Similarly, the 72%-82% mortality in patients who have sustained tissue destruction or surgery is comparable to the experience reported elsewhere in wounded patients[16] and in patients with surgical complications or head injury.[33] Division of Swann and Merrill's cases into these etiologic categories reveals the same pattern (transfusion hemolysis and obstetrical complications in 27 cases, with a mortality of 30%; oliguria after surgery or extensive trauma in 30 patients, with a mortality of 70%; the remaining 28 patients, classified as following nephrotoxic agents or miscellaneous causes, had a mortality rate of 43%). Guild, Young, and Merrill have recently reviewed their cases of carbon tetrachloride poisoning and found a mortality rate of 25%.[30]

Reasons for these differences in mortality are not clear. While the extent and distribution of the tubular lesions is known to vary according to etiologic background,[7] this is of doubtful clinical significance. Our groups are too small to detect significant differences in the severity of the renal damage, but it is improbable that such differences alone would explain the variations in survival rates even if the renal lesions were more extensive in the surgical and traumatic groups. Such factors as disease in other organs, the presence of devitalized tissue, increased portals of entry for infection, and above all the accelerated catabolic response are equally as important as the extent of the renal damage in determining eventual outcome of any case. These complicating factors and their effect upon the metabolism of urea, potassium, and phosphorus have been stressed, especially by Meroney[34,35] and Parsons and McCracken.[20]

Other Factors in Mortality

Age and Sex.—There appears to be no correlation between mortality and age. The difference in mortality between females (34%) and males (68%) is probably due to the preponderance of females in the etiologic groups with the lower mortality rates.

Duration of Disease.—The mean duration of oliguria in patients who survived was 9.5 days (range 1 to 16). In the patients who survived oliguria but died in the diuretic phase the mean duration of oliguria was 10.3 days (range 4 to 18). While these figures do not differ significantly, our clinical impression is that the duration of oliguria has an inverse relationship to survival.

Of all the fatalities, 42% occurred during the diuretic period. In three patients (Cases 4, 11, 36), who died between the 28th and the 75th day after onset of renal failure, the BUN had fallen almost to normal levels, and in four other cases (Cases 24, 63, 95, 99) a peak urinary volume had been reached and the BUN was falling. This emphasizes the fact that recovery is not assured when diuresis begins.

Preexisting Renal Disease.—In 18 patients the initial history or laboratory studies before the development of acute tubular necrosis suggested that chronic urinary tract disease had been present. The evidence for this ranged from a history of lower urinary tract obstruction to known chronic urinary tract infection with renal insufficiency. The mortality rate in these patients was 78%. However, since most of these patients were in the high-mortality groups, it is not possible to assess accurately the influence of previous renal disease on prognosis. Nevertheless, individual case analyses suggest that a prolonged and more complicated course ensues.

Of interest is Case 68, a 64-year-old man who developed acute tubular necrosis after sulfonamide therapy for pneumonia in 1943. Recovery was uneventful, but in January, 1957, a second episode of acute tubular necrosis developed as a complication of nephrectomy for an infected renal cyst. Postmortem examination, besides revealing severe wound infection and a perinephric abscess at the operative site, showed acute tubular necrosis with evidence of a regenerative change in the remaining kidney, but no obvious chronic renal disease was evident. To our knowledge, there are no previous reports of patients who have sustained two episodes of tubular necrosis.

Incidence and Importance of Complications

All of these patients developed the symptom complex of "uremia" to a greater or less degree. The specific complications to be discussed are a part of, or accompany, that symptom complex and should not be thought of as isolated or unconnected incidents that appeared during the clinical course. We have, however, chosen to discuss separately some which appeared to be of greatest importance in the management and prognosis of these patients.

Infection.—Infection was the most frequent complication observed. It was also the severest, accounting for more deaths than any other complication. Eighty per cent of all patients manifested some evidence of infection during the course of their disease. In 27 the infection was minor, such as cystitis or a superficial wound abscess. In 53 it was of major consequence, consisting of one or more of the following types: pneumonia, tracheobronchitis, septicemia, peritonitis, deciduitis, or parotitis. In 11 of these patients severe infection preceded acute tubular necrosis.

Infection was the primary cause of death in 16 patients. In an additional 20 patients whose deaths were attributable primarily to other causes, severe infection was present at the time of death or shortly before. Thus, infection played a major part in 72% of all deaths.

TABLE 3.—*Incidence of All Infections and of Major* Infections in Patients in Various Etiologic Groups*

Etiology	Patients in Group, No.	Patients with Any Infection, %	Patients with Major Infection, %
Surgical complication	32	84	66
Trauma	6	50	33
Transfusion hemolysis	24	79	42
Obstetrical complication	16	87	50
Nephrotoxin	9	67	44
Miscellaneous	13	85	62
Total	100	80	53

* Major infection includes septicemia, pneumonia, peritonitis, tracheobronchitis, or deciduitis.

Table 3 presents statistics on sites of infection and incidence according to etiologic background of the renal disease. The highest incidence of *major* infection occurred in the surgical and miscellaneous groups; the lowest, in the hemolytic transfusion and nephrotoxic groups, suggesting some correlation between incidence of infection and degree of initial tissue damage.

Lungs: Of the major infections, pneumonia and/or tracheobronchitis was the most frequent, occurring in 40% of all patients and accounting for death in seven. In most cases pneumonia occurred relatively late in the course of the renal disease, usually during the diuretic phase. The clinical environment in which pulmonary infection developed was often one characterized by coma and complete exhaustion of the patient. Common predisposing factors were loss of ability to cough or to change body position voluntarily, drying of pharyngeal mucosa from constant mouth breathing, formation of inspissated mucous plugs, and the aspiration of such plugs or vomitus.

Abdomen: Intra-abdominal infections occurred in 25 patients, including 8 whose infection was limited to the pelvis. These patients were mainly in the surgical and obstetrical groups. Four patients died primarily from this complication; all had diffuse peritonitis subsequent to abdominal surgery.

Blood Stream: Septicemia, proved by blood culture or autopsy findings, occurred in 12 patients and was considered responsible for death in 5. By far the highest incidence was observed in the obstetrical group; of nine cases of abortion (eight criminal, one spontaneous), septicemia occurred in six. In all these cases a pelvic infection was assumed or proved to have preceded septicemia. In the six nonobstetrical cases, septicemia developed subsequent to or simultaneously with infection elsewhere.

Urinary Tract: Approximately one-third of all patients developed an infection of the urinary tract. No deaths were attributed to

this complication per se. A thorough study of predisposing factors was not conducted; however, it is of more than casual interest that all but two of these patients had undergone bladder catheterization early in the oliguric phase, usually with a retention catheter. This danger has been stressed in other recent publications.[36,37]

Other Sites: Other identifiable infections were as follows: parotitis (two cases), cellulitis (two cases), perianal abscess (one case).

Comment: Our experience with infection in acute tubular necrosis is not unique. In the previously mentioned review of experience from several renal centers,[22] it was found that in 342 fatal cases infection was the primary cause of death in 28%. Unfortunately, not only does the acutely uremic patient appear more susceptible to bacterial invasion, but, once started, the infectious process is extremely difficult to control. The response to antibiotics is generally poorer than that of the nonuremic patient, in our judgment.

Therapy of this complication is discussed later. We wish to point out here, however, that, until more is known about the mechanism of this vulnerability, therapeutic efforts will probably remain empirical and ineffective. The few studies which have been attempted to assess the influence of renal failure on natural defense mechanisms against bacteria, have failed to show impairment of antibody response, of complement production, or of leukocyte phagocytosis.[38,39] Data are not available for the evaluation of the effectiveness of antibiotics when given either prophylactically or upon specific indication.

Leukocyte Response: Although other authors have noted the occurrence of a "leukemoid" reaction,[8] it is not generally recognized that leukocytosis is the rule rather than the exception and, therefore, that the white blood cell count does not yield accurate information as to the presence or absence of infection. White blood cell counts were recorded in 92 patients. The highest count at any time during the illness, irrespective of the presence or absence of infection, ranged between 7,500 and 97,100. Only two patients had a maximum count of less than 10,000; forty-six had counts exceeding 20,000, and eighteen had counts exceeding 30,000. The higher counts bore no relation to the eventual outcome of the patient. In general, the highest counts occurred during the first week of oliguria.

Hyperkalemia.—Five patients (Cases 5, 12, 25, 39, 87) died from potassium intoxication. The first died before an artificial kidney was available at this institution. The remaining four died while being prepared for dialysis.

The incidence of hyperkalemia was very much higher. Forty-one per cent of patients showed an elevation of serum potassium to more than 7.0 mEq. per liter sometime during the oliguric or early diuretic period, and most of these had electrocardiographic disturbances severer than mild T-wave peaking, e. g., marked increase in T-wave amplitude, lengthened QRS duration, diminished to absent P-waves, or even more pronounced conduction defects.

The rate of rise of the serum potassium has important implications not only with regard to the potential danger of cardiac arrest but also as a reflection of the catabolic response of the patient. The source of the increased extracellular potassium (in the absence of exogenous intake) is the intracellular potassium which is either released from necrotic cells or from viable tissue as a consequence of altered transport mechanisms. Anoxia and acidosis are important factors which cause net flux of potassium from cells.[40] The average daily rise of the serum potassium above the mean for our laboratory has been calculated for each of the patients in the series during the first seven days of oliguria (Table 4). It will be seen that the mean rate of rise was higher in the surgical and traumatic etiologic groups than in the groups with a lower mortality rate and that in each etiologic group the rate of rise was higher in the patients who died than in those that survived. In

TABLE 4.—*Average Daily Rate of Rise of Serum Potassium During Oliguric Period*

Etiologic Group	mEq/L/Day		
	Total	Fatal Cases	Surviving Cases
Surgical complication	0.31	0.35	0.21
Trauma	0.63	0.64	0.56
Transfusion hemolysis	0.20	0.26	0.18
Obstetrical complication	0.29	0.35	0.27
Nephrotoxin	0.23	0.38	0.04
Miscellaneous	0.17	0.18	0.17
All groups	0.28	0.35	0.20

the traumatic group, the average daily rate of rise of 0.6 mEq. per liter is comparable to the figure in high mortality groups reported by other authors.[16,33]

Cardiopulmonary Complications.—Cardiopulmonary complications other than those of infection developed in 49% of patients and were primarily responsible for death in 12. These included cardiac arrhythmias, congestive heart failure, and a peculiar syndrome resembling pulmonary embolism clinically but not pathologically.

Cardiac Arrhythmia: Abnormal cardiac rhythm not attributable to potassium intoxication developed in 18 patients and included atrial fibrillation, coupling, varying degrees of atrioventricular block, ventricular fibrillation, and cardiac arrest. One-half of these patients had a history of cardiovascular disease before the development of renal failure. Four patients (Cases 4, 15, 69, 84) died of sudden ventricular fibrillation or cardiac arrest. Two of these had undergone commissurotomy for chronic rheumatic valvulitis; however, the remaining two had no history of previous cardiac disease.

Twelve of the eighteen patients were receiving digitalis either because of long-standing congestive failure or atrial fibrillation or because of the development of pulmonary edema during the oliguric period. Digitalis toxicity, as evidenced by coupling, supraventricular tachycardia, or ventricular tachycardia, developed during dialysis in five of these and during the diuretic period in two as the serum potassium concentration was falling.

Congestive Heart Failure: Thirty-one patients developed one or more of the following manifestations of congestive failure: dyspnea, orthopnea, systemic venous engorgement, gallop rhythm, crepitant basilar rales, or frank pulmonary edema. More than one-half of this group gave no history of previous cardiac disease, and the fluid balance records in many instances indicated that overhydration had occurred during the early part of the oliguric period. In the majority of cases, congestion responded favorably to various measures, including marked fluid restriction, digitalization, and the removal of water by ultrafiltration during dialysis. However, four patients died of pulmonary edema. Two patients (Cases 7, 51), one of whom had long-standing hypertensive cardiovascular disease, died of frank congestive failure and pulmonary edema, in association with definite overhydration during the oliguric period. The other two patients (Cases 44, 66) died of pulmonary edema, although just prior to its development they appeared to be dehydrated. In retrospect these latter two patients probably were overhydrated because of overestimation of extrarenal fluid losses.

The incidence of overhydration and pulmonary edema in patients referred to us has decreased markedly over the past three years—from 32% prior to 1956 to 15% subsequently. This gratifying change is due in large measure to wider recognition of careful restriction of fluid intake as a cardinal principle in therapy.

Acute Respiratory Failure: Three patients (Cases 46, 57, 64) who died suddenly and unexpectedly presented a clinical picture that was diagnosed in each instance as "probable multiple pulmonary emboli." The same terminal course has been observed in three other uremic patients not included in this series. This course consists of apprehension, tachypnea, hypotension, and occasional respiratory wheezing and later progressive cyanosis and death, all occurring within a few hours. Patient 46 complained of pleuritic chest pain before lapsing into

unconsciousness. In two patients, electrocardiograms and serum potassium determinations a short time before death did not reveal any marked change. In all patients, intake of fluid and sodium had been restricted and hypertension was not prominent. Administration of oxygen, spasmolytic agents, digitalis, and vasopressors had no effect. At postmortem examination careful dissection revealed no evidence of pulmonary emboli and the tracheobronchial tree and lung parenchyma seemed free of changes except for mild to moderate terminal congestion. Gross and microscopic examinations of the heart were negative. This picture may be similar to that described by Swann and Merrill [8] as pulmonary congestion without evidence of fluid and sodium overloading, the result of a process as yet undefined.

Central Nervous System Disturbances.—It is difficult to assess the importance of central nervous system abnormalities as a cause of death. On the basis of clinical evidence alone death was attributed to this cause in only one patient (Case 84), who died suddenly during a generalized convulsion. However, central nervous system disturbances are extremely common, the two most important being coma and convulsions.

Coma: The development of increasing lethargy, drowsiness, and somnolence, common to both the acute and chronic uremic state, was almost universal in this series. More profound alterations in consciousness, to the point of disorientation, were noted in 63 patients. Of these, 32 were semicomatose or comatose sometime during the course of their disease (exclusive of terminal coma). The importance of this complication is illustrated by the fact that almost two-thirds of the comatose patients developed pneumonia in contrast to only 28% of those who did not develop coma. Other difficulties which arose in the unconscious patients were decubitus ulcers, aspiration of vomitus, tracheal obstruction, and urinary retention or incontinence in the diuretic phase, necessitating in some cases the use of indwelling catheters.

Attempts to define the biochemical disturbances responsible for central nervous system depression have not been successful, although such compounds as phenols and guanidine have been implicated at one time or another.[41] Blood ammonia levels have not been greatly elevated in the absence of liver failure,[42] and, while the serum magnesium is usually elevated during oliguria,[43,44] the clinical importance of this is unknown. The role of various organic acid fractions is under investigation.[45]

Convulsions: Generalized convulsions occurred in 27 patients. These developed during the oliguric period in 12 and during the diuretic period in 15 patients. Probably the greatest danger from convulsions stems from the associated anoxia with accentuation of an already threatening hyperkalemia.

In some patients seizures definitely seemed to be related to the administration of whole blood or of sodium solutions. Hypertension may have played a part in others. There was no correlation seen between convulsions and the degree of hypocalcemia. In fact, convulsions were accompanied by definitely positive Chvostek's sign in four patients at a time when the total serum calcium concentration was greater than 8.4 mg. %. Incessant convulsions were abruptly interrupted during dialysis in three patients (Cases 10, 32, 75), suggesting the etiologic role of a "dialyzable" biochemical abnormality. However, in the majority of patients who convulsed the responsible factor could not be identified.

Other Central Nervous System Symptoms: Among other changes seen were restlessness, acute delirium, agitation, and not infrequently extreme fright. Although it is impossible to draw the line between the more marked of these states and a full-blown psychosis, 12 patients exhibited mentation or behavior definitely psychotic in type. Two patients exhibited an intensification of a previous paranoia or reactive depression. Paranoid delusions were occasionally noted. A number of patients developed marked withdrawal during the diuretic phase, and two patients developed a schizophrenic pat-

tern with loss of affect, withdrawal, muteness, and transient catatonia. We have recently seen the latter picture develop after dialysis in three patients, not reported here. These mental aberrations cleared rapidly with further recovery of renal function in all cases but one.

Bleeding.—Defective coagulation is recognized as a common complication of both acute and chronic uremia.[46-48] In this series, 49% of patients bled at some time during their illness exclusive of the period during or immediately following dialysis. In 36, the bleeding was considered significant in that treatment was required or dialysis was withheld or postponed. Death in five cases was due to bleeding. In three of these (Cases 26, 42, 93) intra-abdominal bleeding developed within 4 to 17 days after abdominal surgery. One patient (Case 4) developed an erosion of the esophageal artery on the 10th day of oliguria. Another (Case 99) developed a massive subarachnoid hemorrhage in the diuretic period.

The experience at the Renal Insufficiency Center, in Korea,[16] indicated that while bleeding frequently appeared or was intensified by the heparin administration during dialysis, in only two patients did this necessitate stopping dialysis. In our experience, five patients were denied dialysis (which was otherwise indicated) because of the severity of gastrointestinal or abdominal bleeding. In four other instances dialysis was postponed for 24 to 72 hours for the same reason, and two dialyses were stopped before optimal biochemical results could be achieved because of an accentuation of bleeding. In addition, 15 patients, who had bled previously, developed accentuated blood loss during or immediately after dialysis.

The clotting mechanisms were analyzed 87 times in 47 patients. These tests included determinations of clotting time, one-stage prothrombin time, prothrombin consumption, accelerator globulin, recalcification time, platelet count, clot retraction, and heparin titration. In addition, tests of thromboplastin generation and heparin sensitivity[49] have been done more recently. Forty of the forty-seven patients demonstrated abnormal "coagulograms." A summary of the abnormal findings in the tests is shown in Table 5. It can be seen that a lowered prothrombin consumption and an increased sensitivity to heparin occurred in over two-thirds of patients studied.

The data in these patients and in patients with chronic uremia have been analyzed by Wurzel.[50] Although the measured defects were frequently severe enough to cause spontaneous bleeding, no major statistical differences in these coagulation factors were found between bleeding and nonbleeding patients. This suggests that other factors, such as capillary fragility, may play a major role in this complication.

Delayed Wound Healing.—In this series there were five cases of partial or complete dehiscence of abdominal incisions, occurring

TABLE 5.—*Summary of Coagulation Defects as Measured by Various Tests*

Test	Limits of Normal	Patients Tested, No.	Patients Showing Abnormal Values, No.		Abnormal, %
			Patients Bleeding at Time of Test	Patients Not Bleeding at Time of Test	
Heparin sensitivity	Control	16	3	9	75
Prothrombin consumption	>20 sec.	47	16	16	68
Platelet count	>100,000	47	12	6	38
Thromboplastin generation test	Control	10	2	1	30
Clotting time (in glass)	<20 min.	47	9	4	28
Heparin titration	<.20	26	5	2	27
One-stage prothrombin	>50%	47	9	2	23
Accelerator globulin	>50%	41	6	3	22
Clot retraction		47	4	2	13

from 4 to 15 days postoperatively. In two of these major surgical repair was necessary. Six patients developed fistulae after abdominal surgery. One patient bled slowly from an aortic graft for five days after surgery and eventually died of a massive hemorrhage. A common occurrence was the healing of cut-down sites by secondary rather than primary intention.

These data lend support to the impressions of others, that tissue repair is defective in patients with uremia.[16,51] This defect probably plays a part in the speed of recovery of all patients with acute renal failure not only in the repair of traumatized or infected tissue but also in the rate of renal tubular regeneration. Contributory factors include infections, depletion of labile protein stores, and possibly the biochemical abnormalities of uremia.

Treatment

It is not the purpose of this paper to outline in detail the management of acute renal failure. However, there are several points which should be raised with respect to the prevention and treatment of the complications described.

Infection.—Efforts to decrease the high mortality and morbidity from infection have, of course, included the application of vigorous medical and surgical principles to already established infections. But the greatest salvage of life in these patients will probably stem from prophylaxis against infection; this requires constant surveillance and careful attention to details of good medical and nursing care. Some of the measures which we feel are most important are the following:

Care of Respiratory Tract: We consider such care to be one of the most important facets of management. In the alert patient, such measures as deep-breathing exercises, "blow-bottles," and frequent forced coughing are stressed. If lethargic or comatose, the patients are turned from side to side regularly and hot or cold mist inhalations are provided for the purpose of loosening tenacious secretions. Tracheal aspiration must be vigorous when indicated, and bronchoscopy and tracheostomy must not be considered desperate "last-ditch" procedures.

Special Mouth Care: In the absence of good oral hygiene the mucosa of the mouth and posterior pharynx tend to become dehydrated and crusted with mucous secretions. This, in turn, predisposes to ulceration, bleeding, parotitis, and not infrequently aspiration of infectious material into the lungs. It is the physician's responsibility to stress the importance of careful mouth care to the nursing staff.

Mobilization: Physical activity is urged within the patient's tolerance during the acute stage of the disease and as early in convalescence as is practicable.

Catheterization of Urinary Bladder: This procedure is to be avoided whenever possible because of the danger of inducing urinary tract infection. Unfortunately the initial reaction of many physicians is to place an oliguric patient on constant bladder drainage, presumably because of the importance of accurate daily fluid balance records. But the hazard of underestimating fluid output during oliguria is more than outweighed by the hazard of infection. As the urinary volume reaches a significant level, most patients will be able to void spontaneously. In our opinion, the only absolute indication for catheterization is lower urinary tract obstruction.

Antimicrobial Agents: Infection must be treated boldly with specific agents as determined by in vitro testing, but these agents should not be used indiscriminately in the absence of a specific indication. Our experience suggests that patients with acute renal failure have a higher than average incidence of drug sensitivity, particularly to penicillin. Further dangers of prophylactic antibiotic therapy are (1) the emergence of resistant bacterial strains, (2) candidal infections, and (3) staphylococcal enteritis. Unique to the oliguric state is the development of toxic effects from high tissue concentration of agents usually eliminated by the kidney.

Streptomycin is the drug which offends most in this regard: however, it is not absolutely contraindicated provided the dose is markedly reduced.[52,53]

Hyperkalemia.—Temporary measures were used when indicated for the reduction of the serum potassium level or for treatment of cardiac toxicity. These measures included intravenous administration of hypertonic glucose with insulin, calcium gluconate, and sodium lactate. Longer-lasting effects were noted when potassium was removed from the body. This was done in 46 patients by the oral or rectal administration of cation exchange resins. The mean drop in serum level 24 hours after 50-75 gm. of resin was 0.6 mEq. per liter. In two patients (Cases 2, 3), previously reported,[54] the potassium removed by enemas containing 50 gm. resin daily amounted to 21 to 73 mEq. per day, but the quantity removed varied with the ability of the patient to retain the enema. Hemodialysis, however, remains the most efficient method of removal of potassium.

Congestive Heart Failure.—As stated previously, recognition of the necessity for fluid restriction in these patients has already led to decreased incidence of this complication. Under average conditions of environmental and body temperatures, normal hydration in the adult patient can be maintained by the daily administration of approximately 600 ml. of fluid in addition to measured loss.[13] When extrarenal losses are excessive, however, great difficulty in estimation of fluid requirements may be encountered. Under such circumstances accurate daily weights provide a more reliable index of fluid balance.

The most effective form of treatment of congestive failure, when present, is further restriction of fluid intake, although other methods of treatment are frequently called for. Removal of fluid by ultrafiltration during dialysis has been reported previously [55] and was found to be beneficial in many cases in this series.

The efficacy of digitalization in these patients is difficult to assess. It has been our practice to initiate or continue digitalis therapy in patients with previous heart failure who have shown signs of a recurrence during the course of the acute renal failure. We have also accepted as additional indications auricular fibrillation and congestive failure refractory to fluid restriction. The administration of digitalis must be extremely cautious when a fall in serum potassium concentration is imminent, either as a result of diuresis or of dialysis, because of the recognized potentiation of digitalis toxicity by potassium depletion. It must also be realized that the usual electrocardiographic signs of impending potassium intoxication can be masked by the presence of digitalis.[56]

Bleeding.—Therapeutic attempts to improve blood coagulation were in general disappointing. The use of vitamin K in instances of prothrombin deficiency occasionally reversed the abnormal finding. Bleeding was controlled by the administration of protamine sulfate in three patients (Cases 26, 90, 100) in whom an elevated heparin titer or markedly increased heparin sensitivity was found. Since the most frequent abnormality is in the first stage of coagulation or thromboplastin formation, platelet transfusions, thromboplastic substances, and fresh-frozen plasma are theoretically indicated; in practice these have not been notably effective.

Of special importance is the therapeutic approach to gastrointestinal bleeding. It is generally held that hematemesis or melena occurring in a uremic patient stems from superficial petechial hemorrhage in the stomach or bowel or from multiple uremic ulcerations. Understandably, the attending surgeon is loath to explore such acutely ill patients, especially when it is impossible to predict where the lesion might be, if indeed a single or remediable lesion exists. However, uremia per se does not constitute an absolute contraindication to surgery. It is our feeling that massive and prolonged hematemesis not responding to conservative measures requires surgical exploration. In one case of fatal hemorrhage (Case 1) the site of bleeding was found at autopsy to be

a discrete esophageal erosion. It was felt in retrospect that bleeding could have been checked surgically. In another instance described in the following case report, surgical intervention controlled bleeding.

CASE 11.—A 27-year-old white woman, attempting suicide, ingested bichloride of mercury. Oliguria developed, and she was admitted to the Hospital of the University of Pennsylvania in her third oliguric day. The oliguric phase lasted for 10 days. During this period she was febrile, complained of burning epigastric pain, and produced small amounts of blood-tinged vomitus. A buccal ulceration was noted. Brisk diuresis ensued, but on the 13th day the gastrointestinal bleeding became more persistent and copious. In addition, epistaxis, vaginal oozing, and ecchymoses appeared. The hemoglobin concentration fell to 8.4 gm. % despite multiple transfusions. On the 16th day, after much deliberation a laparotomy was performed, revealing a single bleeding gastric ulcer. Subtotal gastrectomy was done, and thereafter bleeding was not a problem. The patient died of sepsis on her 75th day after onset of oliguria.

Defective Wound Healing.—At present the therapy of delayed wound healing consists mostly of local measures. Traumatic wounds should be carefully debrided before closure. As a rule, skin sutures should not be removed until the patient is well into the convalescent phase. If surgery is performed during the course of acute renal failure, it is wise to close the wound with nonabsorbable (wire) stay sutures.

Recently norethandrolone (Nilevar) has been reported to effect a reduction in the rate of rise of blood urea nitrogen when given late in the oliguric phase of acute renal failure.[67] Some question remains, however, whether this reflection of a decreased catabolic rate is attributable to the drug or to the natural course of the disease. If indeed anabolic steroids prove to be effective in this regard they may provide valuable means of controlling not only delayed wound healing but also other complications relating to accelerated catabolism.

Dialysis

Extracorporeal hemodialysis was performed 69 times on 52 patients. Sixteen patients were dialyzed twice and one patient (Case 50) three times. The interval after onset of oliguria during which the first dialysis was performed ranged from 3 to 14 days, with an average of 8.4 days.

The fact that the mortality rate of dialyzed patients was identical with that of patients not dialyzed (50% in each instance) has no real significance, for the two groups are not comparable from the standpoint of severity of illness. By and large, the patients who were dialyzed were more critically ill than those not dialyzed, according to clinical judgment. In at least one-quarter of the latter group dialysis was not indicated by even the most liberal criteria because of the mildness of clinical and biochemical signs. There is perhaps quantitative evidence that the severity of disease was greater in the dialyzed group when severity is measured by the length of oliguria. The mean duration of oliguria in patients who survived but were not dialyzed was 7.7 days; in the patients who were dialyzed it was 11.5 days. However, it must be conceded that dialysis itself may have prolonged the oliguric period in some cases by reducing the stimulus to osmotic diuresis.[40]

There is also evidence that dialysis is capable of prolonging life. Analysis of the length of survival of all *fatal* cases reveals the median * day of death after onset of oliguria of patients who were dialyzed was 13.5 days, as contrasted to 10.7 days for the patients not dialyzed. In view of the fact that the average dialyzed patient was more severely ill than the average nondialyzed patient, this difference in length of survival seems attributable to dialysis. Teschian reported a similar difference, of 2.1 days average survival time, with and without the use of the artificial kidney.[16]

Unequivocal evidence that dialysis will reduce the mortality rate in this disease must await analysis of larger, well-controlled series of patients with common etiologic background. Perhaps the closest

* The median rather than the average day of death is used because of the wide range (5-82 days) of the length of survival. The average figures are 17.6 days for dialyzed patients and 15.2 days for nondialyzed patients.

approach to this ideal to date was made by Hamburger and Richet.[29] Prior to their use of an artificial kidney, they observed a mortality rate of 75% in 28 patients with oliguria following abortion or intravascular hemolysis. Two years later the mortality rate in a comparable group treated by dialysis was 7%.

The evaluation of dialysis need not rest on survival statistics alone. The experience of others and ourselves attests to the effectiveness of this procedure in relieving many of the symptoms of uremia, such as nausea, vomiting, paralytic ileus, neuromuscular irritability, convulsions, and coma, presumably those symptoms which are due in large part to the retention of dialyzable substances. Moreover, it seems reasonable to believe that if dialysis is performed relatively early in the course of uremia, clinical deterioration may be prevented or delayed sufficiently to avoid some of the serious complications discussed in this paper. For example, if coma and vomiting could be prevented by early, and perhaps repeated, dialysis the risk of pneumonia might be significantly reduced. While our experience with "prophylactic" dialysis has been limited to only recent cases, it has been our impression that most patients so treated are better able to respond to conservative care and are less likely to become serious nursing problems. Consequently, we are inclined to agree with others that this procedure will be most effective when carried out earlier and more frequently than has been generally customary in the past.[14,23,31,40,58]

Summary and Conclusions

A series of 100 cases of acute tubular necrosis observed by us is presented, with an analysis of mortality statistics and of the incidence and severity of complications.

The over-all mortality rate was 50%. We feel that the efficacy of modern management has, at times, been overestimated and that the serious prognosis of this disease needs reemphasis.

The prognosis is related to the setting in which tubular necrosis develops. The mortality rates in patients who developed the disease after transfusion hemolysis or an obstetrical complication were 29% and 25%, respectively. In contrast, over 72% of patients died who developed tubular necrosis as a complication of surgery or trauma.

There was a high incidence of complications, and these contributed greatly to the mortality figures. Eighty per cent of all patients developed some evidence of infection, and this complication was primarily responsible for one-third of all deaths. Other common complications were potassium intoxication, cardiac arrhythmias, congestive failure, central nervous system disturbances, bleeding, and delayed wound healing. Their incidence and importance are discussed.

Certain aspects of therapy are reviewed primarily in relation to prevention or treatment of these complications.

Hemodialysis was carried out in 52 cases. While it is difficult to evaluate the effect of this procedure on mortality statistics, we agree with others that it is a valuable therapeutic adjunct. Some reasons are discussed for believing that earlier and more frequent dialysis may decrease the incidence of complications.

Further improvement in prognosis will depend upon more effective measures for preventing and treating the complications associated with this disease. This in turn will require a better understanding of the mechanisms by which the sudden loss of renal function predisposes to these complications.

We are greatly indebted to the many referring physicians, and to the Hospital of the University of Pennsylvania house staff and nursing staff for their cooperation and help in caring for these patients. Special acknowledgment is made of the contribution of the nursing staff of the Metabolic Unit and of Mr. James Mitchell of the Chemical Section of the Department of Medicine to the hemodialysis program.

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Deaths from Bites and Stings of Venomous Animals and Insects in the United States

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Every year in the United States one learns from newspaper and radio reports of human deaths resulting from injuries by venomous animals and insects. Also, one encounters occasional but dramatic reports of some of these deaths in medical journals. However, the time-honored case-report and review-of-the-medical-literature methods failed to indicate the magnitude of this problem and the animals and insects most frequently involved in these accidents.

Mortality from bites and stings of venomous animals and insects throughout the world is a greater problem than is generally realized by most people. Swaroop and Grab,[1] of the World Health Organization, estimated that there are 30,000 to 40,000 deaths from snakebites alone throughout the world each year. The same authors presented data to show that in some countries venomous animals other than poisonous snakes may be the chief offenders; for example, scorpions kill more people than snakes do in Mexico each year. In a study of snake-bite mortality in the United States from 1950-1954, I[2] reported a total of 71 deaths, an average of 14.2 deaths per year. However, during this same period there were 215 deaths from all venomous animals and insects. Obviously, venomous animals and insects, other than poisonous snakes, were producing many deaths.

The purpose of this study is to find out what venomous animals and insects produce human deaths in the United States, to determine the magnitude of the problem, to study the geographical distribution of these fatal cases, and to elicit other medical and epidemiological facts about these deaths. Deaths due to "accidents caused by bites and stings of venomous animals and insects" are grouped together under Category E927 in the "International Statistical Classification of Diseases, Injuries, and Causes of Death." One difficulty is that deaths resulting from the bites or stings of centipedes, snakes, bees, wasps, scorpions, and other venomous animals and insects are grouped together in this classification. No previous attempt had been made to study the individual insects and animals causing these deaths.

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Method

The method employed in this study was to analyze the death certificates of all persons in the United States who died from bites and stings of venomous animals and insects for the five-year period 1950 through 1954. These certificates were supplied by the National Office of Vital Statistics, U. S. Public Health Service, Washington, D. C. In addition to listing the cause of death, the death certificates contained the following information: age, sex, race, and occupation of the victim; the state where the accident occurred; the day, month, and year of death; the kind of animal or insect inflicting the injury; in most instances, the place where the accident took place (farm, home, etc.), and the interval of time between the bite or sting and death. Additional information about the snake-bite deaths was obtained from a questionnaire mailed to the physician, coroner, or other official who signed the death certificate.

Venomous Animals and Insects

From 1950 through 1954, there were 215 human deaths from venomous animals and insects. Table 1 lists the animals and insects responsible for these deaths. Among the venomous creatures were rattlesnakes, cottonmouth moccasins, coral snakes, other (unidentified) snakes, honeybees, wasps,

TABLE 1.—*Venomous Animals and Insects Responsible for Fatal Bites and Stings in the United States, 1950-1954*

	No.		%	
Hymenoptera insects		86		40.0
Bees	52		24.2	
Wasps	21		9.8	
Yellow jackets	7		3.2	
Hornets	5		2.3	
Ants	1		0.5	
Poisonous snakes		71		33.0
Rattlesnakes	55		25.6	
Cottonmouth moccasins	2		0.9	
Coral snakes	1		0.5	
Unidentified snakes	13		6.0	
Spiders		39		18.1
Scorpions		5		2.3
Coelenterata, unspecified		1		0.5
Stingaree (sting ray)		1		0.5
Animal or insect, type unknown		12		5.6
Total		215		100.0

hornets, yellow jackets, black widow spiders, unidentified spiders (presumably black widows), scorpions, Coelenterata (probably a Portuguese man-of-war), sting rays, ants, and other (unidentified) insects and animals. It is interesting that centipedes, millipedes, Gila monsters, poisonous fishes, copperhead moccasins and, tarantulas were not reported to produce any deaths during this five-year period. This finding, of course, does not mean that these animals are not poisonous; however, it does indicate that they are not a major source of human deaths in the United States. It is highly significant that of the 215 fatalities, the Hymenoptera (bees, wasps, hornets, yellow jackets, and ants) killed 86 (40%) persons, whereas the poisonous snakes killed 71 (33%) persons and the poisonous spiders killed 39 (18%) persons. Rattlesnakes (Crotalus sp.) were the most deadly venomous animals, accounting for 55 human deaths, but bees were in a strong second place, with 52 fatalities. Insects of the order Hymenoptera must be considered "giant killers," owing to the high toll of human lives they take in relation to their small size.

Victims

There were 215 human deaths during the five-year period 1950-1954, or an average

TABLE 2.—*Race and Sex of Victims of Venomous Bites and Stings in the United States, 1950-1954*

Year	Total Deaths	White		Non-White	
		Male	Female	Male	Female
1950	51	32	12	6	1
1951	49	29	10	6	4
1952	44	24	9	9	2
1953	35	21	9	2	3
1954	36	24	8	3	1
Total	215	130	48	26	11

of 43 deaths per year, from venomous animals and insects. This gives an average death rate of 0.28 per 1,000,000 population per year. As seen in Table 2 there were 51 deaths from this cause in 1950; there were 49 deaths in 1951; there were 44 deaths in 1952; there were 35 deaths in 1953, and there were 36 deaths in 1954. About 2.6 times as many males were fatally stung or bitten as females. This probably reflects greater exposure of males to these venomous creatures because of out-of-doors occupations and recreational habits.

The ages of the victims at time of death are found in Table 3. Approximately 44% of the fatal snake bites were among children and youths less than 20 years of age. Snake-venom poisoning is usually more serious in children than in adults because the ratio of units of venom injected to units of body weight is greater. In addition, surveys of snake-bite cases have shown that children

TABLE 3.—*Age Distribution of Victims of Venomous Bites and Stings in the United States, 1950-1954*

Age at Death, Yr.	Insect or Animal				
	Snakes	Hymenoptera	Spiders	Others	Total
0- 4	16	3	9	7	35
5- 9	7	2	2	4	15
10-19	8	1	3	1	13
20-29	3	5	1	—	9
30-39	7	15	2	1	25
40-49	7	21	3	2	33
50-59	15	23	5	3	46
60-69	4	10	6	1	21
70 & over	4	6	8	—	18
Total	71	86	39	19	215

are frequently bitten.[3-5] In Florida, a study of the incidence of poisonous snake bites showed that 49% of all the bites occurred among young people less than 20 years of age.[6] Part of this high incidence of bites in youngsters can be explained by their natural curiosity and their lack of knowledge about snakes. Similarly, 36% of the fatal spider bites occurred among persons less than 20 years of age. However, published reports of black widow spider bites seem to indicate that less than 25% of all victims fall into this age group.[7-10] A notable exception to the previously described age-at-death pattern from venomous animals and insects is that found for the Hymenoptera victims. For this group the number of deaths due to venomous stings appears to increase with age. Only 7% of the reported deaths from Hymenoptera occurred in persons less than 20 years of age. Although, in general, one would expect children to be stung by insects more frequently than adults, most of the fatal stings occurred in adults. This finding suggests that death probably results from something other than the toxic effects of the venom per se. There is strong evidence to indicate that these deaths result from insect allergy.[11,12] It is difficult to explain why there were not more fatal Hymenoptera stings in children. Perhaps this is related to the age of onset of venom allergy and to the interval of time between insect stings. Possibly other host factors also are involved.

There was considerable variation in the interval between the time of the bite or sting and the time of death for the various groups of venomous animals and insects (Table 4). Although there is a strong fear of immediate death following poisonous snake bites, only three persons died in less than an hour. Fifty (70%) of the patients died from 6 to 48 hours after the bite. The venoms of the North American pit viper snakes (rattlesnakes, cottonmouth moccasins, and copperhead moccasins) are absorbed primarily through the lymphatics and tissue spaces; hence, it usually takes several hours before the full toxic effects of the venom are experienced. By way of contrast, most of the deaths resulting from Hymenoptera stings happened within one hour (usually within 15-30 minutes). Of the 75 deaths from this cause, where the interval between the sting and death was recorded, 66 (88%) died within one hour and 72 (96%) were dead within five hours. The physicians who signed the death certificates usually wrote that death resulted from "anaphylaxis," "shock," "allergy," "heart failure," or "coronary occlusion," following a sting or stings by a species of the Hymenoptera. With the exception of three deaths, which probably resulted from overwhelming envenomation from multiple stings, most of the deaths resulted from anaphylatic shock due to insect allergy. Poisonous spider-bite victims most frequently died 18 hours or more after envenomation. Of the 29 victims in which the interval between the bite and death was known, 19 (65%), died from 18 hours to 7 days after the bite. Only three persons were reported to have died in the first 12 hours. Black widow spider (Latrodectus mactans) venom is thought to spread into the body by way of the lymphatic channels. Generally, local symptoms are noted within the first hour or two, but several hours may elapse before the full toxic effects of the venom are experienced, and these symptoms may persist for one to four days.[13,14] Most of the deaths occurring after the first five

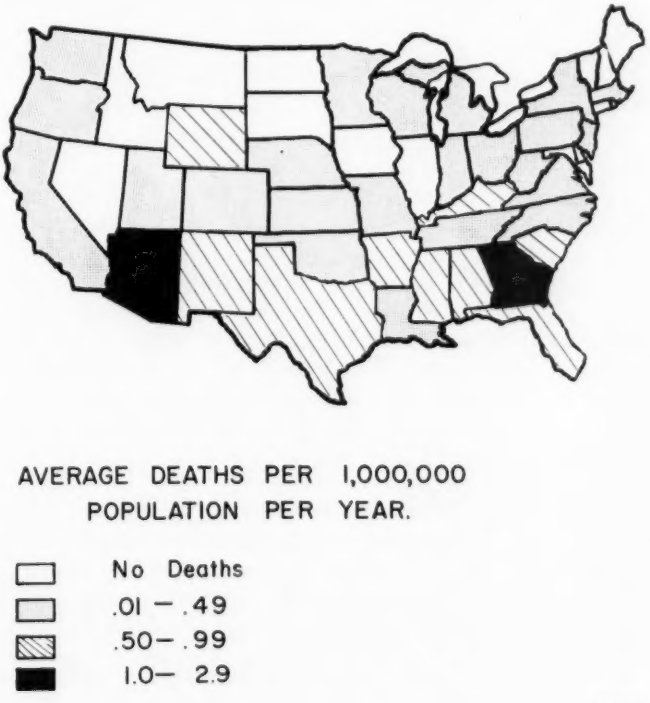
TABLE 4.—*Interval Between Bite or Sting and Death from Venomous Animals and Insects, United States, 1950-1954*

	Offending Animal or Insect				
Interval	Snakes	Hymenoptera	Spiders	Others	Total
0- 1 hr.	3	66	1	3	73
2- 5 hr.	10	6	—	3	19
6-11 hr.	19	—	2	2	23
12-18 hr.	16	—	2	1	19
19-24 hr.	6	—	4	—	10
25-48 hr.	9	1	6	1	17
3- 7 days	5	1	9	2	17
8-14 days	1	1	3	1	6
15 or more days	—	—	2	—	2
Not stated	2	11	10	6	29
Total	71	86	39	19	215

days resulted from complications, such as infection, gangrene, and cerebrovascular accidents. Scorpion-sting victims, a total of five, all died within 12 hours. One of these deaths was attributed to anaphylactic shock resulting from scorpion-venom allergy. The sting ray victim died three days after envenomation, while the interval between sting and death was not recorded for the victim of the coelenterate. The remaining deaths from unknown venomous animals and insects did not exhibit a remarkable pattern for the interval between the bite or sting and death.

Geographical Distribution

Although, in general, venomous animals and insects are more abundant in tropical regions, they are by no means limited to these areas. During the period 1950-1954, deaths resulting from venomous animals and insects were reported from 34 of the 48 states. The states reporting the largest number of fatalities were Texas (36), Georgia (19), California (18), Florida (13), Alabama, Kentucky and North Carolina (10 each), and Arizona (9). A much more meaningful index for measuring deaths due to venomous animals and insects is a death rate which takes into account the population at risk. The average number of deaths per year and the estimated 1952 population for each state and region in the United States were used to calculate the average death rate per 1,000,000 population per year. The highest average death rates per 1,000,000 population were found in the following states: Arizona (2.07), Georgia (1.08), Texas (0.88), Florida (0.84), Mississippi (0.74), Kentucky (0.68), and Alabama, Arkansas, and Wyoming (0.65 each). The geographical distribution of deaths from bites and stings of venomous animals and insects can be seen in the Figure. Note that the northernmost states, especially the New England states, were



Geographical distribution of deaths due to venomous animals and insects in the United States, 1950-1954.

TABLE 5.—*Deaths Resulting from Bites and Stings of Venomous Animals and Insects, by Region and State for the United States, 1950-1954*

Region & State	Animal or Insect				Total Deaths, 1950-1954	Average Deaths/Yr.	Average Deaths/ 1,000,000 Pop/Yr. *
	Snakes	Hymenoptera	Spiders	Others			
New England	—	4	—	—	4	0.8	0.08
Maine	—	—	—	—	—	—	—
New Hampshire	—	—	—	—	—	—	—
Vermont	—	—	—	—	—	—	—
Massachusetts	—	4	—	—	4	0.8	0.17
Rhode Island	—	—	—	—	—	—	—
Connecticut	—	—	—	—	—	—	—
Middle Atlantic	—	8	—	2	10	2.0	0.07
New York	—	3	—	1	4	0.8	0.05
New Jersey	—	2	—	—	2	0.4	0.08
Pennsylvania	—	3	—	1	4	0.8	0.08
East North Central	—	10	1	1	12	2.4	0.08
Ohio	—	4	—	—	4	0.8	0.10
Indiana	—	3	1	1	5	1.0	0.24
Illinois	—	—	—	—	—	—	—
Michigan	—	2	—	—	2	0.4	0.06
Wisconsin	—	1	—	—	1	0.2	0.06
West North Central	2	6	4	—	12	2.4	0.17
Minnesota	—	2	—	—	2	0.4	0.13
Iowa	—	—	—	—	—	—	—
Missouri	1	3	2	—	6	1.2	0.30
North Dakota	—	—	—	—	—	—	—
South Dakota	—	—	—	—	—	—	—
Nebraska	1	—	—	—	1	0.2	0.15
Kansas	—	1	2	—	3	0.6	0.30
South Atlantic	24	17	10	5	56	11.2	0.51
Delaware	—	—	—	—	—	—	—
Maryland	—	—	—	—	—	—	—
District of Columbia	—	—	—	—	—	—	—
Virginia	—	4	1	1	6	1.2	0.34
West Virginia	—	2	—	—	2	0.4	0.20
North Carolina	1	3	5	1	10	2.0	0.48
South Carolina	2	2	1	1	6	1.2	0.55
Georgia	11	4	3	1	19	3.8	1.08
Florida	10	2	—	1	13	2.6	0.84
East South Central	10	13	9	1	33	6.6	0.58
Kentucky	2	5	3	—	10	2.0	0.68
Tennessee	1	4	—	—	5	1.0	0.31
Alabama	5	1	3	1	10	2.0	0.65
Mississippi	2	3	3	—	8	1.6	0.74
West South Central	21	11	13	5	50	10.0	0.67
Arkansas	2	3	1	—	6	1.2	0.65
Louisiana	1	—	3	1	5	1.0	0.36
Oklahoma	—	—	3	—	3	0.6	0.27
Texas	18	8	6	4	36	7.2	0.88
Mountain	6	4	1	4	15	3.0	0.55
Montana	—	—	—	—	—	—	—
Idaho	—	—	—	—	—	—	—
Wyoming	—	1	—	—	1	0.2	0.65
Colorado	—	2	—	—	2	0.4	0.28
New Mexico	1	—	1	—	2	0.4	0.54
Arizona	5	—	—	4	9	1.8	2.07
Utah	—	1	—	—	1	0.2	0.27
Nevada	—	—	—	—	—	—	—
Pacific	8	13	1	1	23	4.6	0.29
Washington	—	3	—	—	3	0.6	0.24
Oregon	1	1	—	—	2	0.4	0.25
California	7	9	1	1	18	3.6	0.31
Total United States	71	86	39	19	215	43.0	0.28 †

* Based on estimated 1952 population for each region and state, published by U. S. Bureau of Census in "Current Population Reports," Series P-25, No. 97, 1954.

† Based on Total 1952 population for the United States.

the ones most often spared of these tragic deaths. However, deaths due to animal venom poisoning are found in every region in this country. Table 5 lists the number of deaths for each group of animals and insects and the death rates per 1,000,000 population for each region and state in the United States. The highest death rates from this cause per 1,000,000 population by region were West South Central (0.67), East South Central (0.58), Mountain (0.55), and South Atlantic (0.51). The lowest death rates were found in the Middle Atlantic (0.07), New England (0.08), and East North Central (0.08) regions.

In general, the states with the highest death rates from all venomous animals and insects also had the highest death rates from poisonous snake bites: Arizona (1.15), Florida (0.65), Georgia (0.63), Texas (0.44), and Alabama (0.32). The high death rate in these states is reflected in the regional incidence of deaths from snake bites. The highest death rates from snake bites were found in the following regions: West South Central (0.28), South Atlantic (0.22), and Mountain (0.22). Stickel [15] has shown that these states and regions are heavily infested with dangerous poisonous snakes, especially rattlesnakes. This finding should not be interpreted to mean that poisonous snake bites occur only in these regions and states. For example, during the five-year period of this study no fatalities from poisonous snake bites were reported for Virginia, Indiana, or Connecticut; however Wood,[4] Minton,[5] and Chotkowski [16] have shown that poisonous snake bites do occur in these states. Indeed, one or more species of poisonous snakes has been reported to inhabit every state in the United States except Maine.

Hymenoptera were reported to cause human fatalities in 29 of the 48 states from 1950-1954. These unfortunate deaths occurred in every region of the country. The regions with the highest average death rates per 1,000,000 population per year were East South Central (0.23), Pacific (0.16), and South Atlantic, West South Central, and Mountain (0.15 each). The widespread distribution of these deaths is in keeping with the finding that species of Hymenoptera (bees, wasps, hornets, yellow jackets, and ants) are prevalent in all of these regions.[17]

Deaths resulting from poisonous spider bites were reported from 16 of the 48 states. The regions with the highest average death rates per 1,000,000 population were West South Central (0.17), East South Central (0.16), and South Atlantic (0.09). No deaths were reported from the New England and the Middle Atlantic regions. However, one must keep in mind the fact that arachnidism is frequently misdiagnosed.[9,10] Thorp and Woodson,[18] in a review of the literature of black widow spider poisoning in the United States from 1726-1943, reported 1,291 cases occurring in 32 states, with 55 deaths in 17 states. The Latrodectus spiders are considered by most authorities [18,20] to be the only poisonous spiders in the United States. However, the bite of a tarantula may prove very painful,[21] and the Loxosceles reclusus spider of Missouri may produce a necrotic lesion.[22] The best-known member of the Latrodectus spiders is Latrodectus mactans, the "black widow" spider. According to Levi [23] there are three species in America: Latrodectus geometricus, the cosmotropical brown spider; Latrodectus mactans, the black widow spider, and Latrodectus curacaviensis. One or more species of Latrodectus spiders has been reported indigenous to every state in the United States. The evidence presented in this study would seem to indicate that deaths from arachnidism are commoner than previously realized.

Scorpionism was reported to have caused five deaths in this country from 1950-1954. Four of these fatal stings occurred in Arizona and one in Texas. According to Stahnke [24] there are about 40 species of scorpions in the United States, of which only Centruroides sculpturatus and Centruroides gertschi are known to possess lethal venom. These deadly species are found

mostly in Arizona and neighboring states. Stahnke [25] reported that scorpions kill more people in Arizona than do the poisonous snakes.

Both of the deaths resulting from the stings of marine venomous animals happened in Texas, along the Gulf of Mexico. However, Russell and his associates [26] report that sting ray injuries are rather common in California coastal waters.

Seasonal Variation

Closely associated with the geographical distribution of fatal bites and stings is the seasonal incidence of these accidents. One might expect some variation in the monthly incidence of bites and stings in the various regions of the United States, but these regional differences should not obscure the seasonal distribution for the entire country. Table 6 shows the number of deaths, by months, resulting from snakes, Hymenoptera, spiders, and other venomous animals and insects.

The number of fatal snake bites increased beginning about April and reached a peak during August and September. Thus, 57 (80%) of the 71 fatal snake bites occurred during the six-month period from April through September. Contrary to popular belief, most snake-bite accidents do not occur during the hunting season. A similar seasonal distribution for nonfatal poisonous snake bites has been observed in several regions of the United States.[3-6] Poisonous snake bites probably are more frequent during the warmer months because snakes are more active at this time and man experiences greater exposure to them through out-of-doors recreation and occupations.

TABLE 6.—*Seasonal Distribution of Deaths Due to Bites and Stings of Venomous Animals and Insects in the United States, 1950-1954*

Month	Animal or Insect				
	Snakes	Hymenoptera	Spiders	Others	Total
Jan.	1	1	2	—	4
Feb.	2	—	2	1	5
March	5	2	3	—	10
April	7	4	5	3	19
May	7	5	3	3	18
June	8	14	6	1	29
July	10	18	2	4	34
Aug.	14	21	4	4	43
Sept.	11	11	4	—	26
Oct.	6	9	4	1	20
Nov.	—	—	3	2	5
Dec.	—	1	1	—	2
Total	71	86	39	19	215

Fatalities resulting from the stinging insects of the order Hymenoptera (bees, wasps, hornets, yellow jackets, and ants) are more frequent during the warmer months. As seen in Table 6, there were few deaths from insect stings during the winter months. The greatest incidence was during the five-month period from June through October, when 73 (85%) of the 86 fatal stings occurred. This seasonal variation reflects both the activity of man and the activity of the insects. Usually hornets, wasps, yellow jackets, and bumble bees die during the colder months, with only the queen surviving the winter to start a new colony the following spring. While honey bees maintain their colony during the winter months, they are confined to their hives for the purpose of clustering to maintain warmth.[17] Thus, only during the spring, summer, and early fall are there large numbers of active, stinging insects to come in contact with man. During this same time man is exposed to the stinging insects through occupations on the farm and in the out-of-doors. Also, man is more likely to be in the yard, garden, and woods at this time.

Bites from poisonous spiders (presumably, all Latrodectus) which resulted in deaths occurred during every month of the year. Since there were only 39 spider-bite deaths from many regions of the country, the seasonal distribution of bites was not defined clearly. However, 23 (59%) of the 39 fatal bites happened during the six-month period from May through October. Bogen,[8] of California, and Kirby-Smith,[9] of Tennessee, collected large series of black widow spider (Latrodectus mactans) bites

and noted that most of these accidents happened from May through October. This seasonal distribution of bites is consistent with the life history of the black widow spider. The female of the species is responsible for most cases of envenomation in humans. The female survives the winter, while most male spiders die. She lays her eggs the following spring and early summer, and the prevalence of young and mature black widows is greatest during the late summer and early fall.[14,18-20] This seasonal increase in spiders coincides with a rise in the number of cases of arachnidism.

Of the five deaths from scorpion-venom poisoning, three occurred in April; one, in December, and one, in February. This seasonal incidence of fatal scorpion stings is not in keeping with the usual seasonal incidence of stings. Stahnke[24] noted that scorpion stings were most frequent during the summer months in Arizona, although bites may occur during every month of the year. The fatality resulting from a sting ray and the death from a coelenterate sting happened during July, when swimming was popular.

Comment

Although animal venom poisoning is an important medical and public health problem in areas such as India, South America, and Africa, this problem has received little attention in the United States. On the basis of this study it would appear that venom poisoning is much commoner than formerly recognized; however, it could hardly be classed as a major medical problem. Previous estimates of the number of bites and stings by venomous animals and insects probably are far too low.

Klauber[27] reviewed previous estimates of snake bites and, on the basis of his own extensive knowledge, estimated that there are about 1,500 poisonous snake bites per year in the United States. However, most of the previous estimates of the incidence of snake bite were based on sources such as newspaper clippings, case reports collected in an unsystematic fashion, and report forms which were enclosed in packages of snake antivenin. Recently I[6] found there were at least 120 cases of snake venom poisoning per year in Florida alone. One would expect large numbers of snake-bite cases each year in Georgia, Alabama, South Carolina, Louisiana, Mississippi, Arkansas, Texas, New Mexico, Arizona, and California. However, there are no reliable statistics to confirm this impression. I would think that most adult deaths from snake bites are certified correctly. On the other hand, there probably is some under reporting of snake-bite deaths among children, where an adequate medical history is lacking.

A totally unexpected and alarming finding in this study was the large number of human deaths resulting from stings by the Hymenoptera. It seems possible that these stinging insects may cause many more deaths per year in this country than indicated by the present study. Swinny[28] pointed out, "Anaphylaxis from insects is not generally known to the profession or to coroners." He cited a death from this cause which was listed on the death certificate as "natural cause unknown." Very likely some sudden deaths from insect allergy, occurring during the warmer months of the year, are certified as "heart attacks" (myocardial infarcts, coronary thrombosis) or "heat strokes." The sting of a single venomous insect in a hypersensitive patient may be sufficient to produce death. The local reaction to the sting may be overlooked or not assigned any importance by the physician or coroner signing the death certificate. Very little is known about the incidence or age of onset of insect allergy but this type of allergy probably is very common.

Deaths from black widow spider bites are much commoner than previous reports indicate.[7,8,18] Bogen and Loomis[29] reviewed the literature on spider bites in the United States up to 1936 and reported 615 cases with 38 deaths, a case fatality rate of 6%. Thorp and Woodson[18] cited 1,291 cases with 55 deaths (a case fatality rate of 4.3% in this country from 1726-1943). Yet in

the present study there were 39 spider-bite deaths reported for a five-year period, 1950-1954. Obviously, the review-of-the-literature method of studying this problem grossly underestimated its magnitude, because usually only serious cases and cases in which the diagnosis was made were reported. This method would also tend to overstate the case fatality rate. For example, Bogen [30] stated that about six spider-bite cases per year for the past 30 years have been treated at the Los Angeles County Hospital, without a single fatality. A diagnosis of arachnidism is difficult to make for a person unfamiliar with the "black widow spider syndrome." This condition is often confused with an "acute surgical abdomen." Very likely many spider-bite deaths were certified as abdominal conditions, and the added insult of an operation may have contributed to the death of these persons.

Since venomous insects and animals are found in every state in the United States, it behooves a physician to find out which species are indigenous to his state, to become familiar with the clinical manifestations of venom poisoning, and to keep up with the latest therapy used for treating these venomous bites and stings.

Summary

This death certificate analysis of all deaths in the United States from "accidents caused by the bites and stings of venomous animals and insects" for the five-year period, 1950-1954, shows there were 215 deaths from this cause, an average of 43 deaths per year, and an average death rate of 0.28 per 1,000,000 population per year.

Of the 215 deaths from venomous animals and insects, the Hymenoptera (bees, wasps, hornets, yellow jackets, and ants) killed 86 (40%) persons, poisonous snakes killed 71 (33%) persons, and poisonous spiders killed 39 (18%) persons. Other animals and insects causing fatalities were scorpions, sting rays, Coelenterata, and unidentified venomous insects and animals. The rattlesnakes (Crotalus sp.) were the most dangerous venomous animals, accounting for 55 deaths, while the bees were next most deadly, taking 52 human lives.

Males were fatally bitten and stung about 2.6 times as often as females. The very young, 1-19 years of age, died of snake and spider venoms most frequently, whereas adults were the most frequent victims of stings by the Hymenoptera. Usually several hours elapsed between the snake and spider bites and the victims' deaths. By way of contrast, 88% of the deaths from Hymenoptera stings happened within one hour after the sting. These deaths were attributed to anaphylaxis resulting from insect allergy.

Deaths from venomous animals and insects were reported from 34 of the 48 states. The highest average death rates per 1,000,000 population were found in the following states: Arizona (2.07), Georgia (1.08), Texas (0.88), Florida (0.84), Mississippi (0.74), Kentucky (0.68), and Alabama, Arkansas, and Wyoming (0.65 each). These fatal venomous bites and stings were reported from every region of the country. These findings are consistent with the geographical distribution of the animals and insects which caused them.

Fatal bites and stings inflicted by poisonous snakes, poisonous spiders, and stinging insects (Hymenoptera) occurred oftener during the warmer months of the year, from April through October. This high incidence of deaths during the warmer months reflects changes in the life histories of the animals and insects and the more out-of-doors exposure of man through occupations and recreation.

On the basis of this study it would appear that previous estimates of the incidence of bites and stings by venomous animals and insects are far too low. Very likely, many deaths in the United States from venomous animals are attributed to other causes on death certificates.

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Single-Disk Antibiotic-Sensitivity Testing of Staphylococci

An Analysis of Technique and Results

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With the increasing number of antibiotics available and useful for the treatment of infectious diseases, the development of accurate and simple methods to determine the antibiotic susceptibility of micro-organisms is of increasing importance. The most widely used method at present is the paper-disk sensitivity test. The more cumbersome tube-dilution technique is valuable in special instances in which bactericidal as well as bacteriostatic end-points are needed. Other procedures, such as the plate-dilution, agar-well-diffusion, or ditch-diffusion technique, are more difficult, offer no advantages for routine use, and have been more or less abandoned.

In spite of its widespread use there exists considerable variability in the performance of the disk technique, leading to a large number of confusing reports in the literature. There are two methods of performing and interpreting the test. In the first, two or three disks containing different concentrations are used for each antibiotic. The presence or absence of a zone of inhibition of growth, without regard to its size, is used to determine susceptibility. For example, a definite zone of inhibition around the lowest-concentration disk indicates that the organism is sensitive, whereas absence of a zone with the highest-concentration disk indicates resistance. Various gradations between these extremes are used to indicate a partial degree of susceptibility and are called "slightly sensitive" or "moderately resistant." This is the method recommended by manufacturers of commercial disks [1,2] and is the one used by the vast majority of the laboratories in this country.

The second is the single-disk method, which uses only one disk for each antibiotic, and the degree of susceptibility is based on the size of the zone of inhibition around the disk. An important advantage is that it is possible to test the sensitivity of a micro-organism to 10 or 12 antibiotics on a single, large (14 cm.) Petri dish.[8] This method is widely used abroad,[3-7] and those who have employed it in this country have found a good correlation between zone sizes and the degree of susceptibility of bacteria.[8-10] However, the manufacturers of commercial disks have been unwilling to include in their instructions a description of the performance and standard zone sizes for the single-disk method, and therefore adequate information concerning this procedure is not available to most laboratories. The reluctance to include such instructions is presumably due to the widespread opinion that, because of variations in inoculum size, media, etc., as the tests are performed in the average laboratory, zone sizes are not a reliable criterion of susceptibility.

The single-disk method has been used at the King County Hospital since 1952, and good correlations with tube-dilution tests and with clinical results have been previously reported [8] for the years 1952 to 1955. Additional data, indicating the superiority of the single-disk method, have been accumulated and will be summarized in the present report, which is based on tests of

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more than 2,000 strains of staphylococci isolated from clinical material.

Methods and Materials

Disk Method.—The technique of the single-disk method has been described in detail in our earlier report.[8] A few colonies of the test organism are picked into 3 ml. tryptose phosphate broth and incubated for about 90 minutes at 37 C. Growth from the broth is streaked over the surface of a 14 cm. Petri dish with a sterile cotton swab, and after 5-30 minutes disks are placed on the surface of the agar, 3 or 4 cm. apart. Only the highest-concentration disks (Difco) are used. Mueller-Hinton agar (Difco) is routinely used in our laboratory because it is free of sulfonamide inhibitors and certain other substances, such as the phosphates, which in some commercial media influence markedly the action of several antibiotics. Although a few other media have similar favorable qualities and provide adequate growth for the majority of micro-organisms, it is important for each laboratory to use a single medium, with standards established for that medium. There are no two media which give identical zone sizes because different binding capacities for antibiotics, different pH, etc. lead to different rates of diffusion. After overnight incubation, the total diameter of the zone of inhibition is measured; this includes the disk, which is 6 mm. in diameter. A recorded zone size of 20 mm. indicates, for instance, that the distance from each border of the disk to the margin of growth is 7 mm. Measuring the entire diameter of the inhibition zone gives greater speed and accuracy, and the error in measuring is small. All single-disk sensitivity tests reported in this study were done as routine laboratory procedures at the King County Hospital from 1955 through 1958.

Tube-Dilution Method.—Tube-dilution tests were performed as described in the earlier study,[8] with use of tryptose phosphate broth and final antibiotic concentrations of 1μg., 2μg., 5μg., 10μg., 25μg., 50μg., and 100μg. per milliliter or units per milliliter. The inoculum was 0.5 ml. of a 10^{-2} dilution of an overnight broth culture. The final volume in each tube was 1 ml. (0.5 ml. inoculum and 0.5 ml. antibiotic in broth). Complete macroscopic inhibition of growth after incubation for 18 hours was interpreted as the end-point.

Micro-Organisms.—This study deals with results obtained with strains of staphylococci, isolated in a routine diagnostic laboratory over a four-year period (1955-1958). This micro-organism was selected as a model because of the large number of sensitivity reports available in the laboratory files, the relative clinical importance of this species, and the unpredictable variations in susceptibility to commonly used antibiotics.

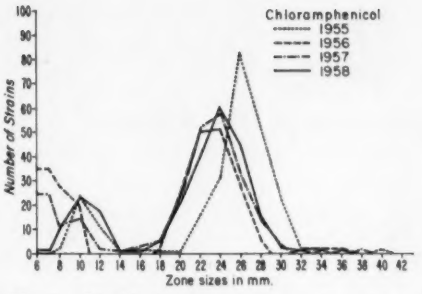

Fig. 1.—Distribution curves of zone diameters of 1,000 strains of staphylococci tested for chloramphenicol susceptibility (250 strains each year). Note the clear-cut resistant and sensitive groups and the stability of division lines over a four-year period.

Results

Chloramphenicol.—Zone diameters of 1,000 coagulase-positive staphylococci are shown in Figure 1. The first 250 strains cultured and examined in the hospital laboratory, beginning July 1 in each of four years (1955-1958), are included. The results of the 250 strains from each year are presented in curves, with the vertical axis indicating the number of strains and the horizontal axis the zone sizes in mm., from 6 (no zone) to 42 mm. It is evident that there are two clearly separated groups, one sensitive and the other resistant. The gap between the two groups extends from zone size 13 through 17 mm., and the few strains found with these zone sizes are called "intermediate." Only 10 intermediate strains were encountered among the 1,000 strains shown in Figure 1. Single-disk results were compared with tube-dilution test results with 108 strains, and the correlations are shown in Figure 2. The vertical axis indicates the minimum inhibitory concentration (MIC) with the tube-dilution, and the horizontal axis, the zone sizes with the single-disk method. Each circle represents the results obtained for a single strain with both tests. The correlation between the two tests was good with 105 of the 108 strains. Strains with a zone size of 12 mm. or less had an MIC of 50μg. per milliliter or greater, and strains with zone sizes of 18 mm. or more required 25μg. per milliliter or less for

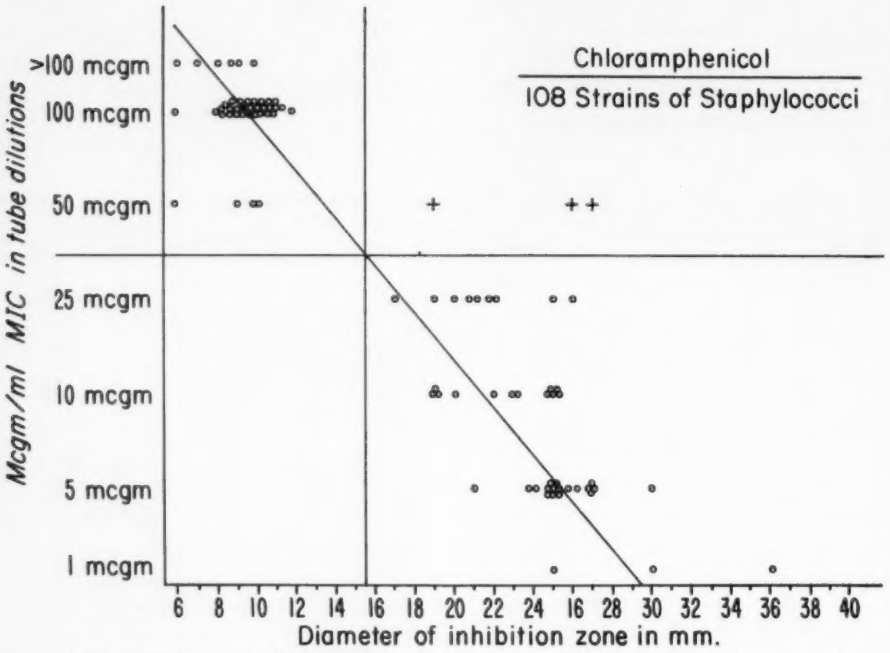
Chloramphenicol
108 Strains of Staphylococci
Mcgm/ml MIC in tube dilutions
>100 mcgm
100 mcgm
50 mcgm
25 mcgm
10 mcgm
5 mcgm
1 mcgm
6 8 10 12 14 16 18 20 22 24 16 28 30 32 34 36 38 40
Diameter of inhibition zone in mm.

Fig. 2.—Results of tube-dilution and single-disk tests of 108 strains of staphylococci. The correlation was good in 105 instances.

inhibition in the tube-dilution tests. Strains with zone sizes between 13 and 17 mm., the intermediates, were not available when tube-dilution tests were done. They may represent the results of extremes in inoculum size and might have fallen in the sensitive or resistant group if they had been retested. For the routine laboratory, retesting the intermediates (10 of 1,000 strains with chloramphenicol) would not be burdensome. When tube-dilution tests are compared with single-disk results, as in Figure 2, there is good correlation regarding the quality "sensitive" or "resistant." However, as to the degree of sensitivity or resistance there is little correlation owing to the variations in inoculum size in both methods. This is expressed in Figure 2 in the distance of many of the circles from the ideal correlation line. Another point deserves mentioning. In 1955, the chloramphenicol-sensitivity tests were done with 60μg. disks, while in the following three years 30μg. disks were used. This had little effect on the curves in Figure 1, the average zone size of the sensitive group being only 2 mm. larger than in later years. Thus a 100% variation in disk concentration made no significant difference in the test results. It is apparent that with high-concentration disks considerable variation in potency makes little difference in results obtained. Because of the larger intermediate zone, the 60μg. disk will appear preferable to the 30μg.

From the curves in Figure 1 one can also obtain a rough estimate of the relative resistance of staphylococci to a given antibiotic. The exact numbers for 1958 were 22% resistant, 1% intermediate, and 77% sensitive to chloramphenicol.

Tetracycline.—Figure 3 demonstrates the sensitivity pattern of 250 coagulase-negative and 250 coagulase-positive strains tested in the routine diagnostic laboratory during the summer and fall of 1958. As with chloramphenicol, there was a resistant and a

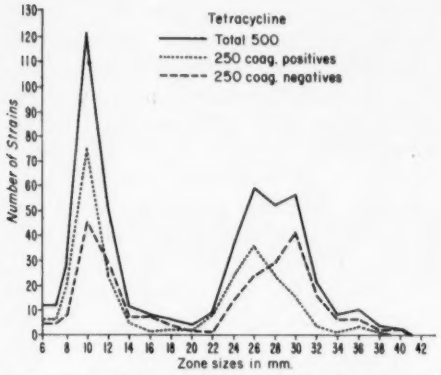

Fig. 3.—Distribution curves of zone diameters of 500 strains of staphylococci tested with 30μg. tetracycline disks.

sensitive group, with a distinct intermediate zone between. The upper curve in Figure 3 includes all 500 strains and has a double peak in the sensitive group, owing to the mixture of coagulase-positive and negative strains. The individual curves for coagulase-positive and negative staphylococci show that the coagulase negatives have a slightly larger mean zone size than the positives, 30 mm. as compared with 26. This is partially owing to the lighter growth of coagulase negatives but probably also reflects a greater inherent susceptibility. Again, the clear-cut division lines, which were obtained by simply plotting the curves and were thus provided by the method itself, were checked with the tube-dilution technique. Fifty strains were tested with both methods, and the correlation was correct in 47 and incorrect in 3 instances. Strains with an inhibition zone of 14 mm. or less had an MIC of 25μg. per milliliter or more, with the majority growing in a concentration of 50μg. per milliliter or more. Strains with zone sizes of 19 mm. or more required only 1μg. per milliliter or less for inhibition in tube dilutions. Since strains with zone sizes between 15 and 18 mm. were rare (about 1 in 200), none was available at the time when the tube-dilution tests were done. Among the 500 strains represented in Figure 3, there were only 12 with no zone of inhibition at all (zone size 6 mm.). According to current recommendations of disk manufacturers, only these 12 would be interpreted as "resistant" and the 213 other strains with small zone sizes would be called "slightly sensitive" or "moderately resistant." The clear-cut differentiation between resistant and sensitive groups, shown in Figure 3, makes it obvious that these terms are inappropriate and give misleading information. Here again, data previously obtained but not presented here have shown that separation of the resistant and sensitive groups is more clear-cut with a 60μg. rather than a 30μg. disk. In 1958, coagulase-positive staphylococci were 53% resistant, 0.5% intermediate, and 46.5% sensitive to tetracycline.

Erythromycin.—Figure 4 shows the sensitivity of 500 consecutive coagulase-negative and 500 coagulase-positive staphylococci tested in the hospital laboratory in 1958. Again, the two sharply divided groups are clearly evident. The coagulase negatives differ from the positives in that they have larger average zone sizes in the sensitive group and that they become much less frequently erythromycin-resistant than the coagulase positives. Of 50 strains examined by both the single-disk and the tube-dilution methods, strains with a zone size of 18 mm. or larger were inhibited by 1μg. per milliliter or less and strains with zone sizes of 13 mm. or less had an MIC of 25μg. per milliliter or more (mostly >100μg. per milliliter). In one case the correlation was incorrect. Two strains fell into the inter-

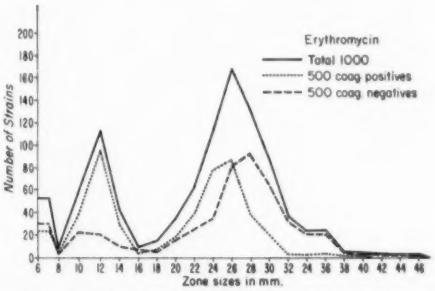

Fig. 4.—Distribution curves of 1,000 strains of staphylococci with a 15μg. erythromycin disk.

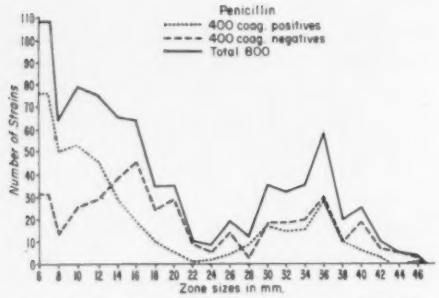

Fig. 5.—Penicillin distribution curves. Resistant strains showed zone sizes up to 20 mm.

mediate group (14-17 mm. zone size). One of them was found to be sensitive with the tube-dilution test, and the other was resistant. Of the 500 coagulase-positive strains, 31% were resistant to erythromycin, 6% were intermediate, and 63% were sensitive.

Penicillin.—The sensitivities of 400 coagulase-positive and 400 coagulase-negative strains tested during the summer of 1958 are shown in Figure 5. Here the differentiation between the sensitive and the resistant groups was not as clear-cut as with the three previously mentioned antibiotics. The intermediate zone is rather broad, extending from 21 to 28 mm. The correlation with the tube-dilution tests (done with 50 strains) was very satisfactory, correct in 46 and incorrect in 4 instances. Strains with a zone size of 29 mm. or more have an MIC of 1 unit per milliliter or less, while strains with a zone size of 21 mm. or less need 5 units per milliliter or more (in most instances >100 units per milliliter) for inhibition of growth with the tube-dilution method. Strains of intermediate zone sizes fall in either group with the tube-dilution test. With penicillin there is a relatively high percentage (up to 10%) of strains within the intermediate zone, and there are two probable reasons. Because the resistant strains are penicillinase producers, they are more sensitive to variations in inoculum size. It is evident from Figure 5 that most of the intermediate strains were coagulase negative. Coagulase-negative penicillinase producers can be resistant as well as sensitive to penicillin in vitro [11] and obviously often fall into the intermediate range. Also penicillin disks deteriorate more readily than most of the other antibiotic disks and in some instances were probably less potent than they should have been. The results for penicillin susceptibility of coagulase-positive staphylococci in 1958 were 77% resistant, 2% intermediate, and 21% sensitive.

Streptomycin.—Results with streptomycin disks were less satisfactory than with any other antibiotic. Many strains fell into the intermediate range, and separation of the sensitive and resistant groups was therefore less clear-cut. A detailed analysis of this phenomenon has shown that occasional variations in potency of disks were at least partly responsible. Some high-concentration (100μg.) disks were found to release less antibiotic than medium-concentration (10μg.) disks. Another reason for a relatively large intermediate group is the fact that, as with penicillin, inoculum size has an important influence on zone diameters. Thus, some sensitive strains are falsely classified as intermediate because of underpotent disks, and an occasional resistant strain falls into the intermediate range because of too light an inoculum. It should be emphasized that in general the potency of disks in the high-concentration series seemed to be well standardized during the

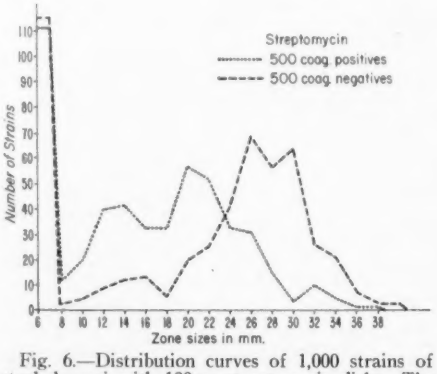

Fig. 6.—Distribution curves of 1,000 strains of staphylococci with 100μg. streptomycin disks. The intermediate zone was less clear-cut than with other antibiotics.

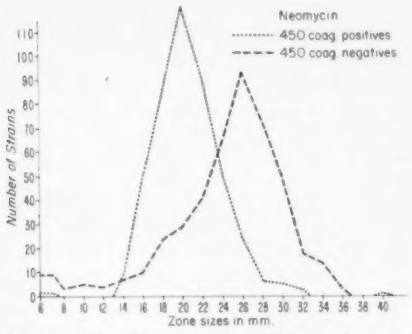

Fig. 7.—Distribution curves of 900 strains tested with 30μg. neomycin disks. Note the difference in susceptibility between coagulase-negative and positive strains.

last four years. Of the 500 strains of coagulase-positive staphylococci consecutively isolated in 1958, there were 56% resistant, 13% intermediate, and 31% sensitive to streptomycin (Fig. 6).

Neomycin.—Susceptibility of staphylococci to the antibiotics so far discussed varied considerably from strain to strain. Neomycin, on the other hand, is an agent to which this species seems uniformly sensitive. Figure 7 indicates the distribution of 450 coagulase-negative and 450 coagulase-positive strains according to their zones of inhibition with a 30 unit neomycin disk. There is a single bell-shaped curve for each of the two groups. Coagulase-negative strains have a much higher average susceptibility than the coagulase positives, the mean zone sizes being 28 and 20 mm., respectively. This may be due in part to lighter growth of coagulase-negative strains on the medium but is attributable chiefly to an inherent difference in susceptibility. A comparison with the next section, on bacitracin, will make this readily apparent. Greer and Menard [12] recognized this difference in susceptibility and used it to distinguish the two groups in a simple manner. They found that coagulase-negative strains showed a zone of inhibition around a 1μg. neomycin disk and coagulase-positive strains did not. In 97% of their cultures this observation correlated well with coagulase determinations. Of the 450 coagulase-positive strains, in Figure 7, only one was neomycin resistant, and this was probably a laboratory error. Among the 450 coagulase-negative strains there were 23 strains with zone sizes of 12 mm. or less. This is surprising, since the coagulase-negative strains as a group are more susceptible to neomycin than the coagulase-positive strains. The most likely explanation is that these organisms were actually streptococci, which are commonly neomycin resistant. Closer scrutiny of neomycin-resistant bacteria in recent months has revealed none that were staphylococci.

Bacitracin.—So far staphylococci have not developed any significant degree of resistance to bacitracin. No resistant mutants were observed, and probably none will emerge. In Figure 8, 300 coagulase-positive and 300 coagulase-negative strains are demonstrated. The distribution curves indicate that both groups have the same average degree of sensitivity, and the peaks of both curves are at zone size 20 mm. Staphylococci have a narrow curve with bacitracin in comparison with the antibiotics discussed earlier. This is probably due in part to relatively poor diffusion, leading to a steep gradient of antibiotic concentration in the agar. An additional factor may be small variations in susceptibility. Variations in degree of resistance or susceptibility, the gradient of antibiotic concentration in the agar (constant for each medium and agent), and variations in inoculum size are the chief

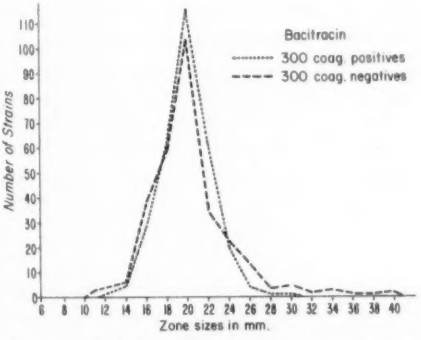

Fig. 8.—With bacitracin there were no resistant strains and coagulase-negative and positive strains showed the same average susceptibility.

factors influencing the width of distribution curves. Highly standardized inocula, a steep gradient of drug concentration in the medium, and little variation in sensitivity of a given species to an antibiotic would lead to a narrow curve, and vice versa. All 600 strains of staphylococci, consecutively isolated during 1958, were bacitracin sensitive.

Comment

The present studies appear to provide convincing evidence of the reliability and practical usefulness of the single-disk technique for performing antibiotic sensitivity tests. To place this evidence in its proper perspective, it is perhaps desirable to consider some of the objections commonly made to the single-disk technique.

The first objection is, "The diameter of the zone of inhibition is not an indication of the effectiveness of the therapeutic agent against the microorganisms."[1] This statement has been made and repeated in various forms[13] in many publications, but we have been unable to find documentation for it. The present studies clearly demonstrate that, in dealing with bacteria isolated in a diagnostic laboratory, there are two clearly divided groups of organisms, one sensitive and the other resistant, and that these two groups are readily separated on the basis of zone sizes. Indeed, the definite intermediate zone which is present between these two groups for most of the commonly used antibiotics is a fortuitous circumstance that is very helpful in diminishing errors due to technical variations. If it were not for this definite intermediate zone, the differentiation between sensitive and resistant organisms undoubtedly would be much more difficult and the single-disk technique would be less reliable because of technical variations. To our knowledge, the clear-cut separation of resistant and sensitive groups, so well shown in this paper in figures constructed from zone sizes, has not been previously demonstrated. However, the phenomenon of a distribution with two peaks was recognized and referred to by Erlanson, in 1951.[11]

A related problem—and one which has led to inaccuracies in reporting results with the multiple-disk method—is the concept that any zone of inhibition, however small, indicates susceptibility. One manufacturer recommends, "Presence or absence of a zone of inhibition surrounding a test disc and not the diameter or area of the zone should be considered to indicate susceptibility of a microorganism."[2] Another recommendation is, "A zone of inhibition of growth around sensitivity discs indicates that the organism is sensitive to the therapeutic agent."[14] A review of the figures presented in this paper shows the incorrectness of this point of view. Definite zones of inhibition are present with a large percentage of resistant organisms with several antibiotics with use of single high-concentration disk, and correlations with tube-dilution tests show that these bacteria are clearly resistant for clinical purposes. With the multiple-disk technique, these resistant strains would be classified as "slightly sensitive" or "moderately resistant." As a result of this improper separation between sensitive and resistant organisms, which is an important defect of the multiple-disk method, numerous articles in the literature have presented data which are very difficult to interpret and in which there has been often too large an intermediate group. In one recent paper,[15] for example, resistance of staphylococci to chlortetracycline was found to decline from 44% to 8% during a six-month period. This was associated with a change to a higher-concentration disk, and so organisms formerly classified as resistant were now considered slightly sensitive because of small zones of inhibition. Numerous other examples of the erroneous classification of intermediate strains could be cited, and these will be described and analyzed elsewhere. Suffice it to say that the arbitrarily established intermediate zone with the multiple-disk method is incorrect in many instances and does not correspond with the dividing points that are delineated in the present paper.

Standards for Interpretation of Single-Disk Sensitivity Tests (High Concentration Disks [Difco], Mueller-Hinton Agar)

Antibiotic, μg.		Zone Diameter, Mm		
		Resistant	Intermediate	Sensitive
Tetracycline	30	6-14	15-18	>18
Oleandomycin	15	6-11	12-16	>16
Chloramphenicol	30	6-12	13-17	>17
Streptomycin	100	6-15	16-19	>19
Penicillin	10 units	6-20	21-28	>28
Erythromycin	15	6-13	14-17	>17
Bacitracin	20 units	6-8	9-12	>12
Neomycin	30	6-8	9-11	>11
Sulfisoxazole	300	6-8	9-14	>14
Nitrofurantoin	300	6-8	9-12	>12

A second objection to the single-disk technique has been that zone diameters cannot be compared because the rate of diffusion of antibiotics is different. The latter is unquestionably true but can be simply solved by setting up different standards of zone sizes for each antibiotic. The standards are actually provided by the method itself, as is clearly demonstrated in the distribution curves in the present paper. Disk concentrations and standards for interpretation as used in our laboratory are presented in the Table. Comparative studies with tube-dilution tests have indicated that these standards are the correct ones for clinical purposes.

The third objection is that zone sizes are unreliable guides, particularly under conditions prevailing in the average diagnostic laboratory, because of variations in composition of media, temperature, duration of incubation, inoculum size, and concentration of antibiotics in the disks. Studies to be reported elsewhere have shown that results with the multiple-disk method are influenced to a greater extent by these variables than are the results obtained with the single-disk technique. The principle reason for this is that inhibition zones are much more susceptible to slight variations in disk potency with low-concentration disks, which are an essential feature of the multiple-disk method. For example, Branch and his group [16] recently examined 60 strains of staphylococci and found that 18% were resistant and 82% moderately resistant to chloramphenicol. Only traces of antibiotic were present in the low-concentration (2μg.) disks, and their failure to give a zone of inhibition led to classification of a high percentage (82%) as moderately resistant strains. An intermediate group of 82%, however, does not exist.

With high-concentration disks, on the other hand, relatively large variations in potency can occur without significantly influencing the results. The minor differences produced with 30μg. and 60μg. chloramphenicol disks (Fig. 1) clearly illustrate this point. Unpublished studies from our laboratory have shown that most high-concentration disks are able to release only a limited amount of their antibiotic content into the medium, giving a large margin of error in case the disk is under-potent. This "safety factor" of the single-disk method has undoubtedly contributed to the consistent results we have obtained over a period of several years.

Curiously, studies comparing single- and multiple-disk methods are not to be found in the literature. Such a study is now being completed in our laboratories. Briefly, it shows that the single-disk method is not only much simpler to perform but is more accurate and less influenced by technical variations than is the multiple-disk method.

Owing to limitations of space, only results obtained with staphylococci have been presented in this paper, but the single-disk method is equally useful for other bacteria.

Summary

Results of antibiotic sensitivity tests, performed in a hospital laboratory with use of a single high-concentration disk for each antibiotic and with measurement of zone sizes to determine susceptibility, are presented for approximately 2,000 strains of staphylococci. A good correlation was noted between the diameter of the zone of inhibition and the degree of susceptibility as determined by tube-dilution tests. Sensitive strains showed large zones of inhibition, while resistant strains had small zones or no zone. Distribution curves constructed

from zone diameters demonstrate that there are two clearly separate groups of staphylococci in the hospital environment, one sensitive and the other resistant, each showing a bell-shaped curve. A definite intermediate zone containing relatively few strains was present between the two bell-shaped curves. This phenomenon was best seen with chloramphenicol, tetracycline, erythromycin, and penicillin but less well with streptomycin. A single bell-shaped curve was present with bacitracin and neomycin, since resistant mutants have not developed.

With a single high-concentration disk it is possible to test the susceptibility of an organism to 10 to 12 antibiotics on a single large culture plate. It is concluded that this method is more economical, simpler to perform, and more accurate than the multiple-disk methods now in use.

Department of Medicine, University of Washington School of Medicine (5) (Dr. Kirby).

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Acute Dissecting Aneurysm of the Aorta

Diagnosis and Selection of Patients for Surgery

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The clinical diagnosis of acute dissecting aneurysm of the aorta has become increasingly important since a method of surgical treatment has been devised and successfully employed.[1-4]

Prior to this, a diagnosis was valuable chiefly for differentiation from other conditions. Diagnosis has always been important prognostically, however, since the mortality of untreated dissecting aneurysm is considerably more than most of the conditions with which it is confused. The clinical picture of acute dissecting aneurysm is protean in its manifestations and may mimic many other conditions. There have been a number of reviews and case reports describing it.*

Since the spontaneous cure of dissecting aneurysm is accomplished by the reentry of the dissecting column of blood into the lumen of the aorta, thus producing a double-barreled aorta,[2,3] surgical treatment was initially devised to accomplish this deliberately. This was done with the hope that the pressure in the false lumen would be decreased and external rupture prevented.

There are now three types of surgical procedures that are employed, depending on the extent and location of the aneurysm:

1. Transection of the aorta, obliteration of the false passage peripherally, then the making of an opening in the intima proximally, allowing blood to enter the true lumen from the false lumen. Reanastomosis is then carried out. This procedure is designed not only to prevent further dissection distally but to allow decompression proximally and lessen the danger of rupture.[8]

2. Direct repair of the aneurysm by suturing of the intimal tear and obliteration under direct vision with the aid of extracorporeal circulation.

3. Resection of the area involved and replacement with a prosthesis. This may be done in conjunction with other operations.[8]

The purpose of this paper is to present the clinical picture of 11 patients with acute dissecting aneurysm of the aorta who underwent surgery at the University of Virginia Hospital.

The symptoms and signs, x-rays, electrocardiograms, and laboratory data were reviewed, and those considered to be critically diagnostic will be discussed.

TABLE 1.—*Age, Sex, and Race*

Age	Male, No.		Female, No.	
	White	Negro	White	Negro
40-49	2			
50-59	2	2		2
60-69	2			
70-79	1			
Total	7	2		2

The age distribution of these 11 patients was from 41 to 73 years; 6 were in the sixth decade and 2 in the seventh decade. There were two patients below 50 years of age and one over 70. Nine were male and two female. Seven of the patients were white, and four were Negro. This age and sex distribution is in keeping with that previously reported in the literature.[5,26]

TABLE 2.—*Mortality*

	No.	%
Died as result of aneurysm	5	45.4
Died of other causes	2	18.2
Recovered	4	36.4

Submitted for publication Dec. 8, 1958.

From the Departments of Medicine and Surgery, University of Virginia School of Medicine.

* References 5, 7, 8, 10, 11, 13, 14, 16, 18, 21, 23, 25, 26.

TABLE 3.—*Location of Pain*

	No.
Substernal, back & left arm	2
Substernal, left shoulder, & epigastrium & back	1
Substernal, arms, & lower back	1
Substernal, lower back, hips, & legs	1
Substernal, epigastric, back, & hips	1
Epigastrium & back	1
Back, between scapulae	1
Midback & lumbar area	1
Lower abdomen & back	1
Epigastrium & right lower quadrant	1

Of the patients who died from causes unrelated to the aneurysm, one died from uremia as a complication of malignant hypertension and one developed a relapse of myasthenia gravis after the operation. The mortality of acute untreated dissecting aneurysm has been previously reported to be from 75%-90%; probably the latter figure is more nearly correct.[4,26]

The pain was very severe in 10 of the 11 patients, more so than is usually encountered in acute myocardial infarction, and it tended to move from the chest to the back or other areas. It resembled that of urinary calculus in two patients.

TABLE 4.—*History of Hypertension*

	No.
Present	7
Absent	3
Unknown	1
Total	11

Seven of the eleven patients reported here were known to be hypertensive prior to the development of the dissecting aneurysm; hypertension was not present in three, and a reliable history was not obtained in one.

Hypertension is reported to be present in the great majority of patients with dissecting aneurysm, particularly in those over 40 years of age.[5,10,11,14,25,26]

TABLE 5.—*Diastolic Murmur*

	No.
Present	5
Absent	6

An early diastolic murmur was heard at the aortic area or at the left sternal border in 5 of the 11 patients. The presence of such a murmur has been previously reported in approximately 25% of patients,[11] varying from 13.4% to 56%.[5,8,25] The cause of the murmur is not clear, but it is probably due to stretching of the aortic ring.[9]

TABLE 6.—*Electrocardiographic Findings*

	No.
Nonspecific T-wave abnormalities	4
Changes indicative of left ventricular hypertrophy	4
Changes suggestive of old infarction	1
Negative T-waves indicative of ischemia	1
Normal	1

The electrocardiogram was abnormal in all but one patient; in none, however, was there evidence of a recent myocardial infarction. Changes indicative of an old infarction were found in one. In four patients there were changes consistent with left ventricular hypertrophy, and in four nonspecific T-wave abnormalities were noted. In one changes indicative of acute ischemia were present, and these reverted toward normal after decompression of the aneurysm. The electrocardiogram of one was normal before and after operation.

Electrocardiographic evidence of myocardial infarction has been found in patients with dissecting aneurysm, presumably due to the involvement of the coronary arteries followed by interference with coronary blood flow and resulting in myocardial ischemia or infarction.[5,10,21]

TABLE 7.—*Abnormal Peripheral Pulses*

	No.
Absent	5
Present	
Diminished right femoral pulsation	2
Absent right femoral, diminished left femoral	2
Diminished right radial & right common carotid	1
Absent, both femorals	1

The abnormalities of the peripheral pulses and difference in blood pressure are due to involvement of the affected arteries in the dissection, and so partial or complete

occlusion of the lumen occurs. It may occasionally be transient, since, as the dissection progresses distally, the particular artery may be decompressed and obstruction relieved. On the other hand, the obstruction may be permanent, with resulting ischemia and necrosis peripherally.

Various clinical pictures may follow such arterial obstruction, depending on the artery involved. Cerebral ischemia may result when the dissection involves the vessels of the aortic arch, and difference in the blood pressure of the upper extremities may be caused by a similar mechanism. Dissection around the celiac axis, the renal arteries, or the spinal arteries will result in abdominal, renal, or neurological symptoms, respectively. When the dissection progresses to the terminal aorta the bifurcation or one of its branches may be affected, with resulting arterial insufficiency of the lower extremities.

TABLE 8.—*Neurological Abnormalities*

Type	No.
Preoperative paralysis & hypesthesia of lower extremities	1
Postoperative weakness of lower extremities	1

In one patient there was complete paralysis of the lower extremities, as well as marked hypesthesia of the thighs and legs. This patient had dissection involving the thoracic and abdominal aorta with complete obstruction of the terminal aorta and both common iliac arteries. The spinal arteries, as well as the peripheral arteries, were probably affected.

One patient developed motor weakness of the lower extremities 24 hours after surgery, without sensory changes. This may have been due to further dissection but probably resulted from interference with the blood supply to the spinal cord during the operation. This has subsequently gradually cleared up.

TABLE 9.—*X-Ray Abnormalities Helpful in Diagnosis*

Type	No.
Dilated aorta	
Ascending arch & descending aorta	2
Ascending arch of aorta	2
Descending aorta	1
Dilated arch & increased heart size with absent pulsations	1
Abnormal aortagram	1
Abnormal I. V. pyelogram	1
Total	8

In eight patients the x-ray examination was helpful in establishing the diagnosis. The aorta was dilated in various portions in six patients, with changes very suggestive of dissecting aneurysm. An aortogram was pathognomic of this condition in one patient in whom a double-barreled aorta could be seen. An increased cardiac shadow which pulsated poorly under the fluoroscopy was indicative of pericardial effusion in one patient, and this led to a pericardial tap which showed the presence of hemopericardium. An intravenous pyelogram showed no excretion of the dye on the right in one patient, whereas two years previously the intravenous pyelogram was normal.

TABLE 10.—*Location of Aneurysm*

	No.
Ascending aorta & arch only	2
Ascending arch, thoracic & abdominal aorta	1
Ascending arch, thoracic, abdominal, & both iliacs	1
Arch & thoracic, aorta	1
Thoracic & abdominal aorta	3
Thoracic, abdominal, & iliac arteries	1
Thoracic, adominal, & right common iliac artery	2
Total	11

Table 10 shows the location and extent of involvement of the aorta by the aneurysm. It can be seen that the ascending aorta and arch were involved in 4 of the 11 patients and the dissection was localized to this area in 2.

The arch and thoracic aorta above were involved once. There was involvement of the thoracic and abdominal aorta alone on

three occasions. The iliac arteries were involved in the dissection in three instances.

Warren, in his review, reported that 54% of acute dissecting aneurysms are located proximal to the descending aorta.[4] This occurred in 2 of the 11 herein reported. Burchell[12] reports, in a review of 22 autopsied cases at the Mayo Clinic, that approximately 70% involved the ascending aorta; 90%, the arch, and 80%, the abdominal aorta.[12]

TABLE 11.—*Site of Rupture*

	No.
Intrapericardial	2
Left chest	1
Peritoneum	1
Total	4

Rupture occurred in four patients after operation, twice in the pericardium and once each in the left chest and in the peritoneum. There was preoperative seepage of blood into the pericardium of one patient, but death was due to invagination of the internal lamina of the sac into the aortic lumen, with obstruction of the vessels of the aortic arch. It has been reported that death of 95% of patients in the acute phase results from external rupture and that 70% of all such cases died from intrapericardial hemorrhage.[14,19] Rapture in the chest is next commonest, but abdominal rupture is rare.[5,11,13,14,17,18,25]

TABLE 12.—*Abdominal Signs*

	No.	
	Present	Absent
Mass	3	8
Bruit	4	7

In three patients a pulsating abdominal mass was found, and in one of these this was thought to be a saccular aneurysm.

TABLE 13.—*Associated Physiological Phenomena*

Type	No.
Syncope	2
Marked transient blood pressure elevation	2
Impairment of function of right kidney on I. V. pyelogram	1
Subacute cardiac tamponade due to hemopericardium	1
Hemothorax	1
Hematoma medial to right scapula 2 mo. before dissecting aneurysm developed	1
Myasthenia gravis, postoperative	1
ECG abnormalities which returned to normal after surgery	1

Syncope ushered in the episode in two patients. In both there was involvement of the aortic arch, and in one of these the innominate and right common carotid were affected. In the first instance the syncope was probably reflex in origin, and in the second, due to cerebral ischemia. The probable mechanisms of syncope were reviewed by Hirst et al.[26]

One patient was admitted with a history of severe pain in the lumbosacral region and concurrently had marked blood pressure elevation. The blood pressure subsequently returned to normal and remained there. Another patient, whose blood pressure had previously been normal, developed hypertension shortly after the pain radiated to the back. This patient had an intravenous pyelogram which showed no excretion of the dye on the right. It was thought that the hypertension in these patients resulted from temporary renal ischemia due to obstruction of a renal artery.

Cardiac tamponade gradually occurred in one patient over a 12-hour period. This was a man who was admitted with severe chest pain and shock. There were only minor electrocardiographic abnormalities and nothing in particular to suggest myocardial infarction or pericarditis. The intensity of the heart sounds gradually diminished; the neck veins became distended; the blood pressure decreased, and pulsus paradoxus developed. Fluoroscopy revealed an enlarged cardiac shadow with no visible pulsations. A pericardial tap was performed, and dark-red blood under low pressure was ob-

tained. The presence of hemopericardium was confirmed at operation.

A large subcutaneous hematoma was found medial to the left scapula in one patient two months before the development of the dissecting aneurysm. This may have been the beginning of the dissecting aneurysm.

Myasthenia gravis developed postoperatively in one patient. This man had a dissecting aneurysm involving the arch and upper descending aorta. A window was made in the intima proximally, and the dissection, sutured peripherally. Orlon was wrapped around the affected region of the aorta. The anesthesia consisted of nitrous oxide, thiopental (Pentothal) sodium, and curare, and Dr. Douglas Eastwood, who was administrating the anesthetic, noted that spontaneous respirations had not begun four hours after completion of the surgery. He suggested that the patient might have myasthenia gravis. A history was subsequently obtained that in 1930 he developed muscular weakness and at that time was thought to have progressive bulbar palsy. This cleared up spontaneously, and, though there were recurrent episodes of mild weakness during the next 15 years, he had no trouble at all during the 5 years preceding the present illness. During this time he worked hard as a farmer and was doing such work when the pain developed which ushered in the present illness. After the operation generalized weakness continued, and, despite the administration of cholinergic drugs and artificial respiration, he died two weeks after the operation. This case was previously reported.[24]

TABLE 14.—*Type of Operation*

	No.
Intimal window & suture of thoracic aorta	5
Intimal window & suture of abdominal aorta & resection of bifurcation	3
Wrapping of ascending aorta with Orlon	1
Decompression, repair of intimal opening, suturing together layers of sac and employment of extra corporeal circulation	2

In eight patients the aorta was transected, the aneurysm decompressed, and an intimal window made in the proximal section. The two layers of the aneurysm were then sutured together, and reanastomosis, carried out. This was done five times in the thoracic and three times in the abdominal aorta. Orlon was wrapped around the aneurysm, which involved the ascending aorta and proximal arch only, of one patient. No other procedure was possible at the time, since extracorporeal circulation was not then employed in this hospital. Since then two patients have been repaired with the aid of a pump.

In one the ascending aorta and arch alone were involved and definitive repair was effected. This patient is well and asymptomatic three months after surgery.

The other patient was thought to have dissection beginning in the upper thoracic aorta just below the left subclavicular artery and extending throughout to the femoral artery. An intimal tear was seen, which was repaired, and the two layers of the sac were sutured together. Circulation to the thoracic and abdominal viscera and lower extremities was carried out by means of an extracorporeal pump, which was connected between the left subclavian and left femoral artery. This patient did well for eight days. On the ninth day a loud to-and-fro murmur was heard at the left sternal border and aortic area, which was consistent with aortic regurgitation. He had no symptoms, and there was no demonstrable change in the aorta on x-ray. Death occurred suddenly 12 days after surgery, and postmortem study revealed that the dissection had extended proximally to involve the aortic arch and ascending aorta. Death was due to rupture in the pericardium.

TABLE 15.—*Follow-Up Time*

No.	Time, Mo.
1	34
1	10
1	5
1	2

One patient each has been followed 34 months, 10 months, 5 months, and 2 months. These are well and active.

Comment

TABLE 16.—*Review of Critical Diagnostic Points*

	No.	%
History of pain	10	91
X-ray	9	82
Absence of ECG changes indicative of myocardial infarction	7	63.6
Difference in peripheral pulses	6	54.5
Diastolic murmur	5	
Abdominal bruit	4	36.4
Abdominal mass	3	27.2
Transient marked blood pressure elevation	2	18.2
Systolic bruit over innominate artery, transient ECG changes indicative of ischemia	1	9.1
Hemopericardium with tamponade	1	9.1
Neurological abnormalities	1	9.1

It can be seen from Table 16 that the history of pain was the most important factor in the diagnosis in 10 of the 11 patients. This was very severe and usually radiated to the back and frequently moved from its original location to another area. The pain was severer than is usually encountered in myocardial infarction.

The absence of electrocardiographic changes to indicate myocardial infarction was helpful in seven patients. In one patient changes indicative of acute ischemia appeared. This helped to localize the aneurysm in the ascending aorta.

The presence of an early diastolic murmur was suggestive on five occasions and was of crucial diagnostic importance in three of these five patients.

There was x-ray evidence of dilatation of the aorta in six patients, and in another an aortogram showed a double-barreled lumen, thus confirming the diagnosis. An increase in the heart size with abnormal pulsations on fluoroscopy was very helpful in another patient. An intravenous pyelogram gave valuable evidence in one.

A difference in the peripheral pulses was helpful in six instances, in five of which the femoral arteries were affected. These findings were of value diagnostically as well as in the determination of the extent of the dissection.

The finding of an abdominal bruit was helpful in three instances and should have been helpful in the fourth; however, it was not interpreted properly and was thought to indicate a saccular aneurysm in this last instance.

The development of an abdominal mass was of diagnostic value in two of the three times it was found, particularly in one which had appeared over an eight-hour period of observation in the hospital.

The development of cardiac tamponade following severe chest pain and accompanied by no specific electrocardiographic abnormalities was diagnostic of dissecting aneurysm in one patient.

The development of transient hypertension with lumbar pain was helpful in two patients, and paralysis and hypesthesia of the lower extremities were of confirmatory value in one.

A systolic bruit developed over the innominate artery on one occasion. This disappeared after surgery was done.

The mortality of acute dissecting aneurysm is very high and has been variously reported to be from 75%-90%.[4,26] The surgical mortality is also high because of the nature of the pathological process which allows it to develop as well as the usually associated vascular complications. With newer surgical aids and techniques, however, this mortality should be considerably reduced. In the present series 7 of 11 patients died, 4 of rupture of the aneurysm despite decompression or repair, and can be considered operative failures. One had an Orlon wrapping around the ascending aorta; since dissection did not extend past the aortic arch, decompression was not possible. Death was due to invagination of the dissected portion of the aorta into the arch. At that time extracorporeal circulation was not employed in this hospital.

Two patients died of causes other than the dissecting aneurysm. One developed myasthenia gravis and, except for this unfortunate complication, had an excellent

chance for recovery. Another patient had malignant hypertension, with very poor renal function prior to the development of the dissecting aneurysm, and died with uremia. Though the dissection involved the renal arteries, decompression was attained, and postmortem examination showed no evidence of renal infarction but only changes due to arteriolosclerotic renal disease. This patient would probably have survived if the previous renal damage had not been so severe.

Of the patients who survived the immediate postoperative period, four are well and one died 12 days postoperatively. One who has marked hypertension has survived three years and works daily as a domestic. The other three are doing well 11 months, 6 months, and 3 months after surgery.

The selection of patients for surgery is not difficult once the diagnosis is made, since surgery offers a much better chance for survival than that of possible spontaneous cure. However, the type of surgical approach depends on the location and extent of the dissection.

One must temper enthusiasm with judgment, and the diagnosis must be reasonably certain before operation is carried out. Patients with severe vascular disease and, in particular, those who have chronic renal insufficiency should not be subjected to surgery. Patients who have electrocardiographic changes indicating myocardial infarction and enzyme studies to support this should not be explored unless there is unequivocal x-ray and clinical evidence of dissecting aneurysm. Other patients in whom there is good reason to believe that a dissecting aneurysm is present should be subjected to surgery as soon as the diagnosis is made, the type of surgery depending on the location of the aneurysm.

Summary

The clinical histories of 11 patients with dissecting aneurysm who underwent surgery were reviewed, and the diagnostic points, emphasized.

Four of these eleven patients survived surgery and are doing well postoperatively. It is believed that two other patients would have survived except for unfortunate complications.

The diagnosis of dissecting aneurysm presents a great challenge, since surgical therapy offers a better chance of survival than spontaneous cure.

Enthusiasm should be tempered with judgment; not only should the diagnosis be assured but the patient should not have other conditions which would prevent survival.

The operation should be done promptly in properly selected patients as soon as the diagnosis is made.

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Appendix

Critical Diagnostic Points, Type of Surgery, and Result for Each Patient

Case 1.—Negro woman, age 55.

1. History of very severe pain in the middorsal lumbar area.
2. Presence of a bruit over the abdominal aorta.
3. Weak right femoral pulse and decreased blood pressure in the right leg.
4. Normal intravenous pyelogram.
5. Aortogram
6. Location—thoracic and abdominal.
7. Type of operation—window and suture.
8. Result—survival, well.

Case 2.—White man, age 49.

1. History of very severe substernal pain radiating to back, hips, and legs.
2. Paralysis of lower extremities with accompanying hypesthesia.
3. Loss of pulsation of vessels of lower extremities.
4. History of hematoma medial to right scapula two months before.
5. Lack of ECG changes indicative of myocardial infarction.
6. Location—thoracic abdomen, both iliacs.
7. Type of operation—window and resection of terminal aorta.
8. Result—died with uremia.

Case 3.—Negro man, age 52.

1. History of severe substernal pain radiating to back and arms.
2. Early diastolic murmur at aortic area and left sternal border.
3. Absence of electrocardiographic changes indicative of myocardial infarction.
4. Enlarged cardiac shadow with poor pulsations and dilated ascending aorta.
5. Signs of cardiac tamponade and finding of hemopericardium by pericardial tap.
6. Location—ascending aorta and arch.
7. Type of operation—wrapping with Orlon.
8. Result—death due to invagination of intima into aortic arch.

Case 4.—White man, age 62.

1. History of sudden severe pain between scapulae, accompanied by shock.
2. Finding of left hemothorax.
3. Absent left femoral pulsation and weak right femoral pulsation.
4. Lack of electrocardiographic changes suggestive of recent infarction.
5. Location—ascending arch, thoracic and abdominal aorta.
6. Type of operation—window and suture.
7. Result—died, rupture in pleura.

Case 5.—Negro woman, age 55.

1. History of severe substernal pain, radiating to the left shoulder, epigastrium, and back.
2. Early diastolic murmur at aortic area and left sternal border.
3. Lack of electrocardiographic changes indicative of myocardial infarction.
4. Absent left femoral and weak right femoral pulsations.
5. Dilated arch and descending aorta on x-ray.
6. Location—ascending arch, thoracic abdomen, and both iliacs.

7. Type of operation—window and suture.
8. Result—died as a result of rupture into the pericardium.

CASE 6.—Negro man, age 56.

1. History of severe epigastric and right lower quadrant pain.
2. Mass in right lower quadrant of abdomen.
3. Early diastolic murmur at aortic area and left sternal border. This was of only secondary importance, since the patient had a history of syphilis.
4. Operation confirmed the diagnosis which was suspected prior to surgery.
5. Location—thoracic abdomen and right common iliac.
6. Type of operation—window suture and resection of bifurcation.
7. Result—died owing to rupture into peritoneum.

CASE 7.—White man, age 73.

1. Diagnosis made at operation.
2. Pain in the lower abdomen and back, accompanied by a pulsating abdominal mass and bruit, were thought to indicate the presence of a saccular aneurysm with leakage.
3. X-ray showed calcification of the abdominal aorta and dilated descending aorta.
4. Location—thoracic and abdominal aorta.
5. Type of operation—window and resection of bifurcation.
6. Result—patient is well and active.

CASE 8.—White man, age 62.

1. History of severe substernal pain radiating to the back.
2. Progressive increase in the size of the arch and upper descending aorta, by x-ray.
3. Lack of electrocardiographic changes indicative of myocardial infarction.
4. Early diastolic murmur at aortic area.
5. Location—arch and thoracic aorta.
6. Type of operation—window suture and wrapping with Orlon.
7. Result—died with myasthenia gravis, postoperative.

CASE 9.—White man, age 59.

1. History of very severe pain in the epigastrium, radiating to the back.
2. Marked blood pressure elevation shortly after onset of pain, subsequently returning to normal.
3. Abdominal mass with bruit.
4. Absence of electrocardiographic changes indicative of myocardial infarction.
5. Location—thoracic and abdominal aorta.
6. Type of surgery—window and suture.
7. Result—patient well and active.

CASE 10.—White man, age 53.

1. History of sudden severe pain in the anterior chest, radiating to arms, elbows, and subsequently to the back, with syncope.
2. Decreased right radial and right carotid pulse and decreased blood pressure in right arm.
3. Electrocardiographic changes indicative of myocardial ischemia, systolic bruit over innominate artery.
4. Location—ascending aorta and arch.
5. Type of surgery—definitive repair.
6. Result—patient is well and active.

CASE 11.—White man, age 41.

1. History of severe lower substernal pain, radiating to the back and hips.
2. Decreased right femoral pulsation.
3. Demonstration of nonfunctioning right kidney by intravenous pyelogram.
4. Dilated aortic arch, on x-ray.
5. Lack of electrocardiographic changes indicative of myocardial infarction.
6. Location—ascending aortic arch, thoracic abdomen, and right common iliac.
7. Type of surgery—attempt at definitive repair with auxiliary circulation.
8. Result—died on 12th postoperative day of rupture into pericardium.

Correlation Between in Vitro Studies and Response to Antibiotic Therapy in Staphylococcic Bacteremia

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The selection of the proper antibiotic is a major problem that faces the clinician who makes the diagnosis of Staphylococcus pyogenes var. aureus bacteremia. The present study was done to determine how helpful the tube-dilution method of determining bacterial sensitivity to antibiotics was in solving this problem.

In vitro antibiotic sensitivity tests have been criticized as inadequate because of the different milieu in which the antibiotic must act in vivo.[1,2] Despite this criticism, many physicians are greatly influenced by the results of commercial disk antibiotic-sensitivity tests that are used in most bacteriology laboratories.[3,4] Previous reports have stressed the lack of standardization of the disk method in testing antibiotic sensitivity of bacterial strains, and there was striking variability in the results reported from different laboratories.[5-8] "False resistance" in many tests has been related to the rates of diffusion and deterioration of the antibiotic and has deprived patients of an effective and possibly curative antibiotic.[9,10] On the other hand, the results of repeated tube-dilution tests have represented a better agreement and less tendency to err toward showing increased sensitivity.[7,11,12]

In the present study, the reliability of the tube-dilution sensitivity test was investigated by a correlation of the result of the sensitivity in vitro by the tube-dilution method with the effect of administration of the various antibiotics to patients with staphylococcic bacteremia. The study also suggested a simplified modification of the tube-dilution method, which will be presented.

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Materials and Methods

Case records of 100 consecutive patients with S. pyogenes var. aureus bacteremia, treated at Milwaukee County Hospital between 1952 and 1957, were studied. Positive blood cultures for coagulase-positive S. pyogenes var. aureus had been obtained at least once on all the patients and more than once on most of them during their acute illness. Most of these cases had been either seen in consultation or treated by one of us (B. A. W.). In each instance in which an antibiotic was administered to a patient, one of three results was agreed upon by the two investigators: (1) "no response," when the patient died on the antibiotic or the blood culture remained positive or the temperature did not drop three days after administration of this antibiotic; (2) "response," when blood culture became negative and the patient was cured; (3) "undetermined response," when a careful examination of the case by the two investigators did not reveal enough evidence for classification as either "response" or "no response."

After this decision was made, the report of the in vitro sensitivity of the S. pyogenes var. aureus to the administered antibiotic was noted.

The tube-dilution sensitivity method had been used on all the cases. A heavy bacterial inoculum (1:100 dilution of an 18-hour culture, which is approximately 1,000,000) was added to the test dilution of antibiotic. The minimal inhibitory concentration was determined by the absence of gross visual turbidity after incubation for 18 hours. The concentrations ranged from 100μg. to 0.38μg. per milliliter. Separate charts were then drawn for every antibiotic, with its minimal inhibitory concentration in micrograms per milliliter obtained in vitro plotted against the type of clinical response, determined as outlined, in every case to whom this antibiotic was administered.

In addition, each instance in which a blood culture was positive when a particular antibiotic was being given was recorded and plotted against the minimal inhibitory concentration of the antibiotic to that particular strain.

Results

The study revealed a definite correlation between the in vitro sensitivity of S. pyogenes var. aureus by the tube-dilution method to the various antibiotics and the clinical response obtained when these antibiotics were administered. The details regarding each antibiotic will be discussed separately.

Penicillin.—Of 81 patients who received penicillin at one time during the course of their illness, 57 had no clinical response, 18 responded, and in 6 cases the response was undetermined (Fig. 1).

All of the cases that responded were sensitive to a concentration of 3μg. of penicillin per milliliter or less, and there was not a single response when the minimal inhibitory concentration (M. I. C.) was higher than this level.

A "clinical level" of sensitivity to penicillin can therefore be considered at an inhibitory concentration of 6μg. per milliliter, above which no response is to be expected, as no "false resistance" was noted. Of the 29 cases who were sensitive in vitro (M. I. C. 3μg. per milliliter and less), 8 did not give the expected good clinical response. An abstract of the eight cases in which there was no correlation revealed that if the virulence of the organism and the altered host susceptibility are taken into account rationalization for their "no response" could be reached (Table 1).

In summary then, if the inhibitory concentration of penicillin by the tube-dilution method in cases of S. pyogenes var. aureus coagulase-positive bacteremia is 6μg. per milliliter and higher, no response should be expected on administration of the drug, as no false resistance was noted. On the other hand, a few cases with M. I. C. of 3μg. per milliliter and less did not respond as expected, but in most of these cases complicating factors could rationalize the therapeutic failure.

Chloramphenicol.—Chloramphenicol was used in 53 cases, and there was a response in only 4 (Fig. 2). The M. I. C. in these cases were 38, 6, 6, and 12μg. per milliliter, which were among the lowest M. I. C.'s noted to chloramphenicol (Fig. 2). This suggests a possibility of a correlation but suggests even more strongly that chloramphenicol was a relatively ineffective drug in this series of cases.

Erythromycin.—Erythromycin was given to 43 patients, and a definite "response" was obtained in 14; "no response," in 23,

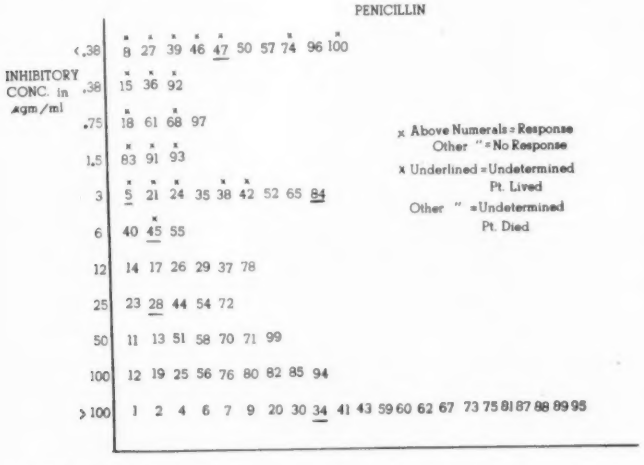

Fig. 1.—Correlation between sensitivity to penicillin and the clinical result. The numbers within the figure correspond to the cases studied. This convention is used in Figures 1 through 5.

TABLE 1.—*"Capsule Summaries" of Cases in Which There Was No Response in Spite of in Vitro Sensitivity of the Staphylococci to Antibiotics That Were Used*

Case No.	Cases in Which No Clinical Response Was Obtained While in Vitro Sensitivity Was at M. I. C. of 3 μg/Ml. & Less	Antibiotics Administered & Their M. I. C., μg/Ml.
35	7 yr. old with congenital cystic disease of lung, staphylococcic pneumonia, & bacteremia	Pen. 3, Strep. 3
50	50-yr.-old diabetic with multiple systemic abscesses, papillary necrosis of kidneys, & pericarditis	Pen. <0.38
52	29-yr.-old with 50% burn; staphylococcic bacteremia developed, also Pseudomonous endocarditis; died	Pen. 3, Eryth. 1.5, Novo. <0.38
57	70-yr.-old with staphylococcic meningitis secondary to otitis media & staphylococcic septicemia	Pen. <0.38, Strep. 3, Chlortet. <0.38
61	64-yr.-old with metastatic carcinoma of gastrointestinal tract & terminal staphylococcic septicemia	Pen. 0.75
65	42-yr.-old cirrhotic with hepatic decompensation; died of terminal staphylococcic septicemia	Pen. 3, Eryth. 1.5, Neo. 0.38
96	76-yr.-old found stuporous at home; developed staphylococcic pneumonia & died; most probably had C. V. A.	Pen. 0.38, Chloram. 0.38, Eryth. 75
97	69-yr.-old with a broken hip; developed wound infection & died in spite of apparent response of fever	Pen. 0.75, Chloram. 3, Novo. 1.5, Vanco, 0.38
49	50-yr.-old diabetic with bacterial endocarditis, osteomyelitis of spine, & meningitis responded only to I. V. novobiocin; died unexpectedly 11 days later	Eryth. 1.5, Novo. <0.38, Neo. 0.38
54	84-yr.-old with cellulitis, eczema, herpes zoster; very septic course; had to be given cortisone, penicillin, erythromycin; died	Eryth. 0.75
30	29-yr.-old white woman died of acute bacterial endocarditis (S. pyogenes var. aureus) 3 days after admission	Strep. 1.5
26	83-yr.-old came for elective transurethral resection; developed bacterial endocarditis & septicemia due to staphylococcus; died	Chlortet. 0.75, Neo. 3
56	2-yr.-old baby with 50% burns; developed staphylococcic septicemia; did not respond to chlortetracycline but did to erythromycin & skin grafting	Chlortet. 0.75
70	40-yr.-old with pulmonary T. B.; entered for segmental resection; had stormy postoperative course with bleeding; needed reexploration; had Staphylococcus in pleural cavity & septicemia	Tetra. 0.38
6	59-yr.-old white man with fractured hip and postoperative wound infection; developed staphylococcic septicemia & died in spite of chlortetracycline, chloramphenicol, penicillin, streptomycin, & finally neomycin	Neo. 0.38
11	46-yr.-old with 30% burns; developed staphylococcic septicemia & died in spite of extensive antibiotic therapy with penicillin, chloramphenicol, erythromycin, & vancomycin	Vanco. 0.38
12	68-yr.-old white man developed acute staphylococcic bacterial endocarditis & septicemia after T. U. R.; died 3 wk. later	Neo. <0.38
48	68-yr.-old with ruptured appendix operated on; subsequent course septic with positive blood & cerebral spinal fluid culture; at autopsy found to have ruptured gallbladder also	Novo. <0.38, Neo. 0.38
71	86-yr.-old man hospitalized with permanent cystostomy tube for 8 mo., developed septicemia with Staphylococcus sensitive only to neomycin & novobiocin; died after 24-hr. treatment with neomycin	Neo. 0.75
25	62-yr.-old man with advanced pulmonary tuberculosis came for follow-up cystoscopy because of previous bladder resections in 1934 & 1953; developed fatal staphylococcic septicemia with renal involvement	Eryth. 3
79	79-yr.-old diabetic had fractured hip & open reduction; developed staphylococcic wound infection, osteomyelitis, & septicemia; died in spite of vigorous chemotherapy	Eryth. 3

and the rest, "undetermined." Eighteen strains had a M. I. C. of 6μg. per milliliter and higher, and none of these responded to therapy with erythromycin. Of 25 strains with M. I. C. of 3μg. per milliliter and less, 7 did not respond clinically and did not correlate with the in vitro sensitivity (Fig. 3). An abstract of these cases reveals that they were extremely poor-risk patients and were sensitive to other antibiotics besides erythromycin, and still no response was obtained.

Thus, with erythromycin the M. I. C. of 6μg. per milliliter can be considered as a level above which no clinical response should be expected.

Streptomycin.—Of 22 cases who received streptomycin, 3 had a clinical response and their corresponding M. I. C.'s were 6, 3, and 0.75μg. per milliliter. Three other cases

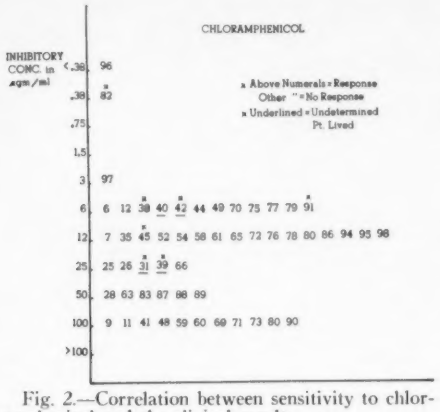

Fig. 2.—Correlation between sensitivity to chloramphenicol and the clinical result.

with low M. I. C. levels (3μg. and less) did not respond as expected, and three were "undetermined" (Table 1).

All of the other 16 cases had resistant sensitivity levels of 6μg. per milliliter and above and correlated with the in vitro sensitivity by lack of clinical response (Fig. 3).

*Tetracycline.**—One of the tetracyclines was used in 41 instances. In 15 there was a response, and sensitivities in these cases revealed M. I. C. of 6μg. per milliliter and less.

In the 17 instances where the M. I. C. was higher than 6μg. per milliliter no clinical response was obtained (Fig. 4). On the other hand, four cases did not respond clinically, although they were sensitive in vitro with respective M. I. C. of 0.75, 0.75, 0.38, and <0.38 (Table 1).

Vancomycin, Novobiocin, Neomycin.—Vancomycin, novobiocin, neomycin were used 25 times, and in only 10 instances was there a clinical "response." It should be pointed out, however, that these antibiotics were used on the extremely ill patients and, especially in case of neomycin, on nearly terminal patients after a trial of other antibiotics. In no case was the M. I. C. more than 6μg. per milliliter, i. e., all the strains were sensitive in vitro, and in 14 instances there was "no response" (Table 1). These findings emphasize the fact that in vitro sensitivity is no guarantee of clinical response.

Composite Results

The results obtained with every antibiotic separately were compiled into one graphic record, in which the different levels of sensitivity of all the strains to all the antibiotics used were plotted against the percentage of clinical responses obtained at every minimal inhibitory concentration (Fig. 6).

This clearly showed that a reliable level for evaluating in vitro whether or not a clinical response can be expected is an in-

* Either chlortetracycline, oxytetracycline, or tetracycline.

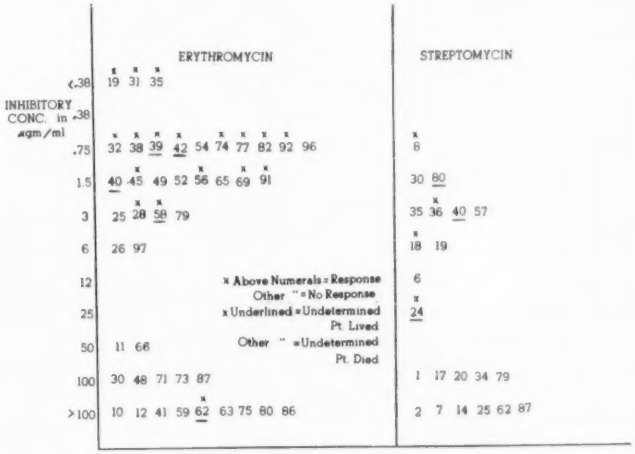

Fig. 3.—Correlation between sensitivities to erythromycin and streptomycin and the clinical result.

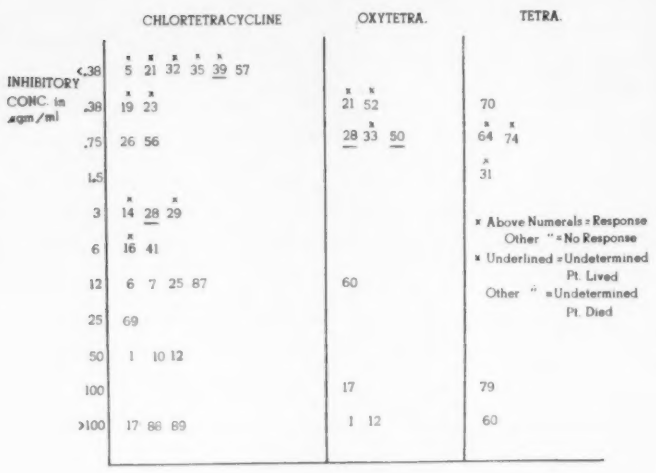

Fig. 4.—Correlation between sensitivities to the tetracyclines and the clinical result.

hibitory concentration of 6μg. per milliliter (Fig. 6). At a level of 6μg. and above, there was a "response" in only 5 patients out of 155, and 4 of them had a M. I. C. of 6μg. per milliliter (Table 2). At the levels of 3μg. and less, 59 good responses correlated satisfactorily with the sensitivity studies, and in 38 instances (21 patients, Table 1), there was "no response." This is in accordance with abundant evidence to indicate that antimicrobial therapy has not been successful in dealing with a number of serious Staphylococcus infections in hospitalized patients in spite of in vitro antibiotic sensitivity.[12,14-20] Thus our therapeutic failures should not be ascribed to drug resistance alone but also to the basic underlying disease upon which Staphylococcus is superimposed and circumstances which lead to altered host resistance.

Sensitivities of Staphylococci Isolated While Patients Were on Antibiotics.—Most of the staphylococci cultured from the patients while they were receiving antibotics were in vitro resistant to those antibiotics (Fig. 7). Positive blood cultures were ob-

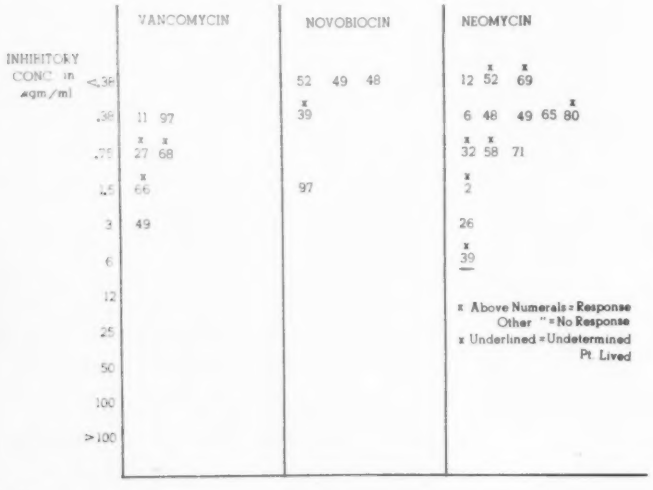

Fig. 5.—Correlation between sensitivities to vancomycin, novobiocin, and neomycin and the clinical result.

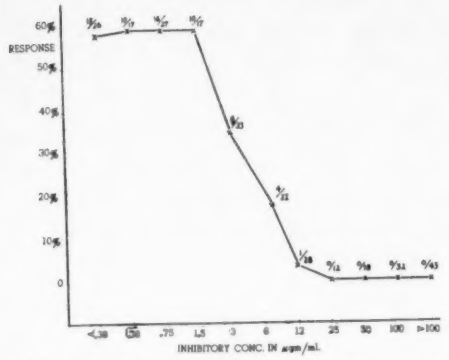

Fig. 6.—Per cent of responses at various inhibitory concentrations of the antibiotics. The denominator in the fractions is the total number of observations and the numerator the number of responses at that particular M. I. C.

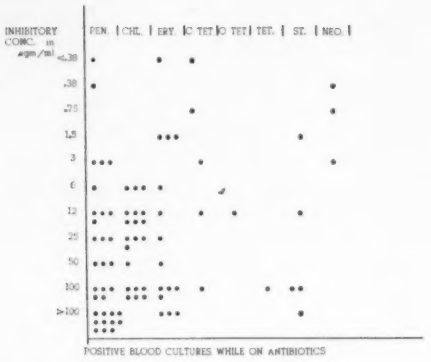

Fig. 7.—The number of blood cultures positive at different sensitivity levels of the various antibiotics.

tained in 66 instances when the M. I. C. was 6μg. per milliliter and more and in only 16 instances when the M. I. C. was 3μg. and less. This constitutes additional evidence of the reliability of the in vitro test for antibiotic sensitivity by the tube-dilution method.

Comment

Perhaps the most important information derived from this study was the distinct correlation between in vitro "resistance" and lack of clinical response when an M. I. C. of 6μg. per milliliter is used as the dividing point (Fig. 6). In only one instance out of 133 trials was a clinical response obtained when the staphylococci grew in a concentration of 6μg. of antibiotic per milliliter. This suggests an alternative method of laboratory testing for those who feel, as we do, that it is not safe to trust a patient's welfare to disk sensitivity tests as they are now done and who feel the traditional tube-dilution method is too cumbersome for general use. This alternative is the use of a single tube dilution containing a final concentration of 6μg. of antibiotic per milliliter. If the organism is resistant to 6μg. of an antibiotic per milliliter, our study suggests practically no chance of response (0.75%). If it is inhibited by 6μg. a therapeutic trial of the drug is justified. Problem cases, of course, would need more extensive studies.

TABLE 2.—*Comparison of Responses*

M. I. C.	Total Responses	Response	No Response	Undetermined
3μg/ml. & less	110	59	38	13
6μg/ml. & above	155	5	140	10

Since we have noted this, we now use at the Milwaukee County Hospital the following technique for our routine studies on staphylococci:

A loop full of organisms is taken from a plate or slant and placed in 10 cc. of dextrose broth (this gives a concentration of around 1,000,000 organisms per milliliter). Care must be taken not to use enough organisms to make the solution turbid. Then 0.5 ml. of this suspension is added to a tube containing 0.5 ml. of distilled water with a concentration of 12μg. of antibiotic per milliliter (this gives a final concentration of 6μg. per milliliter). If there is growth in 18 hours, the organism is reported as clinically resistant. Bactericidal activity can be determined by subculture of 0.1 ml. of the content of the tube in 10 cc. of dextrose broth. Large numbers of tubes containing 6μg. of each antibiotic per milliliter are easily made up and can be stored in a frozen state without loss of potency.[18]

This general plan follows the idea of Kirby[21] in regard to the single concentration of disk but has the general advantages of the tube-dilution method of determining bacterial sensitivity to antibiotics, since combinations of antibiotics can be tested and bactericidal determinations can be made

with slight obvious modifications.[12] Further studies will be necessary to justify this method for use with organisms other than the staphylococci.

Two findings in regard to the use of penicillin in staphylococcic infections also are worthy of emphasis. First, in no case was a clinical response obtained when the organisms were resistant to greater than 3μg. of penicillin per milliliter, even when dosages of penicillin up to 60,000,000 units per day were used. This should discourage the common practice of giving penicillin in serious staphylococci infections in spite of the results of sensitivtiy studies.[22]

On the other hand, responses were not infrequently obtained at sensitivity levels of 1.5 and 3μg. per milliliter (0.9 to 1.8 units). Since staphylococci that are resistant to greater than one unit of penicillin in high dosage inevitably produce penicillinase, our findings suggest that the production of penicillinase by a strain of staphylococci does not necessarily make the strain clinically resistant to the action of penicillin, as has been suggested by others.[23,24]

Summary and Conclusions

One hundred consecutive case records of staphylococcic bacteremia seen at Milwaukee County Hospital were studied, and the clinical responses to the administration of different antibiotics were determined.

The reports of the sensitivities of the staphylococci to the administered antibiotics as determined by the tube-dilution method were examined, and a correlation was made between the results of the in vitro tests and the type of clinical response.

In only one case did a clinical response occur (0.75%) when the in vitro results showed the organism to be resistant to 6μg. of an antibiotic per milliliter, but there was not always a clinical response when the organism was more sensitive. This suggests that the clinician should not give patients the antibiotics to which the infecting staphylococci are resistant in vitro by the tube-dilution method. It further suggests that in vitro sensitivity tests by this method are no guarantee of clinical results and that host factors and complications must be always considered.

The use of a single concentration of 6μg. of antibiotic per milliliter is suggested as a practical modification for the tube-dilution method of determining staphylococcal sensitivity to antibiotics.

Massive dosages of penicillin did not effect a cure in a single instance when the staphylococci were resistant to a concentration of 6μg. of penicillin per milliliter in vitro.

In a few cases staphylococci that were able to produce penicillinase were apparently eradicated by penicillin therapy.

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Myxedema

A Reevaluation of Clinical Diagnosis Based on Eighty Cases

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From the earliest descriptions of cretinism by Paracelsus [1] and Platerus [2] until the definitive contributions of Curling [3] and Gull,[4] in the late 19th century, a great morass of superstition, ignorance, and error had been gradually conquered. Correlation of thyroid atrophy found at autopsy with the clinical state, myxedema,[5] and subsequent successful treatment of this condition with a glycerin extract of sheep thyroid [6,7] provided physicians with one of the most reliable approaches to the complete control of an otherwise crippling disease. It is indeed a paradox that, despite our increasing knowledge of basic thyroid physiology and the development of progressively more accurate assays of thyroid function, recent emphasis is being placed on diagnoses of "hypothyroidism" and the even more obscure entity of "idiopathic hypometabolism," while clear-cut myxedema continues to go unrecognized.

Previous reviews, by Means and Lerman [8] and by Lerman,[9] have emphasized the subtle onset, diverse symptomatology, and diagnostic pitfalls of myxedema. The purpose of this communication is to reappraise these views and, more specifically, to determine the current degree of failure to recognize myxedema, to assess reasons for such oversight, and to offer—on an evaluation of 80 cases—significant points which help to correct this deficiency.

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General Nature of the Study

The charts of all patients discharged from the Georgetown University Hospital and outpatient clinic with a diagnosis of primary hypothyroidism during the period 1947-1957 have been reviewed. Unequivocal clinical and laboratory evidence of thyroid failure, coupled in most cases with clear-cut response to replacement therapy, was present in 80 cases. With six exceptions, each of these acceptable cases had been seen by one of us. These 80 cases were then analyzed as to mode of onset, symptomatology, pertinent physical features, and laboratory abnormalities, with particular emphasis on those features of the disease that had been most helpful in suggesting the correct diagnosis. Myxedema due to hypopituitarism or to suppression of endogenous thyrotropin secretion by the administration of thyroid preparations has not been included. Differential diagnosis of these conditions has been reviewed by others [8-12] and need not be commented on here.

In interpreting these data it became apparent that any list of symptoms elicited from a myxedematous patient is conditioned by two important factors, the patient's unreliability as a historian and the questioner's preordained concept of what constitutes a suitable history for such a patient. Since the present study evaluates the composite findings of several interviewers in each case, these impediments are minimized. However, in most cases, not all possible important clinical features were sought, and the list of symptoms obtained more properly represents spontaneous complaints. In addition, the laboratory study changed with the passage of years and must be interpreted in that light.

Analysis of Cases

Sex and Etiology.—In this series there were 69 female and 11 male patients whose ages at the time of diagnosis ranged from 16 to 73 years. Of these 80 cases, 44 were presumed to have idiopathic atrophy of the thyroid. In another 19 patients, thyroidectomy had been performed from 3 months to 30 years prior to the diagnosis of myxedema

TABLE 1.—*Etiology*

	Cases, No.
Idiopathic thyroid atrophy	44
Prior thyroidectomy	19
Goiter	
Proven Hashimoto's struma	6
Presumed Hashimoto's struma (no biopsy)	6
Riedel's struma	1
External radiation	2
Radioiodine therapy	2
Total	80

and was considered to be either the direct cause or a contributing factor in the development of thyroid failure. An additional 13 patients had goiters; in 6, open biopsy revealed Hashimoto's struma; in 1, Riedel's struma. In the remaining six patients, most of whom were seen in recent years, biopsy was not performed, this decision being based on the opinion that myxedema accompanied by diffuse thyromegaly of moderate degree most likely results from Hashimoto's disease. Myxedema developed after external irradiation to the thyroid in two patients and followed radioiodine therapy in two others. These data are presented in Table 1.

Symptoms.—The subjective manifestations encountered are listed in order of decreasing frequency in Table 2. In general, the nonspecific complaints of decreased energy, intolerance to cold, weakness, inability to concentrate, constipation, and poor memory occurred with great frequency. This may well reflect the enthusiasm with which such "classic" complaints were sought. Much more impressive, however, was the frequency of occurrence of paresthesias of the extremities. Of the 62 patients specifically questioned about this symptom, 57, or 92%, affirmed its presence. Another common complaint, not often sought in patients with myxedema, is muscle and joint pain, at times so severe as to be incapacitating. This occurred in almost one-third of the cases.

Signs.—The most frequently noted objective manifestations of myxedema are listed in Table 3. For a number of years at this hospital particular attention has been paid to the presence of pseudomyotonic or "hung-up" deep tendon reflexes. In the present series, 72 patients were specifically tested for this phenomenon, and its presence was confirmed by at least two observers in 68 patients. Specific mention of the menstrual pattern was made in 21 cases. In 18, or 86%, abnormality of menstruation, usually manifested by increased duration of flow, accompanied the onset of myxedema.

TABLE 2.—*Symptoms*

	Cases, No.	% of Total Cases
Paresthesias	57/62	92 *
Loss of energy	63	79
Intolerance to cold	41	51
Muscular weakness	27	34
Muscle & joint pain	25	31
Inability to concentrate	25	31
Drowsiness	24	30
Constipation	22	27
Forgetfulness	18	23
Emotional lability	12	15
Decreased auditory acuity	12	15
Headaches	11	14
Dysarthria	11	14
Dizziness	10	12
Blurred vision	6	8
Fullness in throat	6	8
Pain in the anterior neck	5	6
Tinnitus	4	5
Loss of libido	3	4
Nasal congestion	2	3
Ptyalism	2	3

* Refers to percentage of patients specifically questioned.

TABLE 3.—*Signs*

	Cases, No.	% of Total Cases
"Pseudomyotonic" reflexes	68/72	95 *
Change in menstrual pattern	18/21	86 *
Dry, scaly skin	63	79
Puffy eyelids	56	70
Hoarse voice	45	56
Weight gain	33	41
Dependent, pitting edema	24	30
Sparse axillary & pubic hair	24	30
Pallor	19	24
Thinning of eyebrows	19	24
Yellow skin	18	23
Loss of scalp hair	14	18
Abdominal distention	14	18
Goiter	13	16
Decreased sweating	8	10
Weight loss	5	6
Unsteady gait	4	5

* Percentage of patients specifically tested or questioned.

Weight gain, although encountered frequently, was seldom more than 15 lb. and usually only 7 to 8 lb. This abnormality could be documented rather accurately in those patients in whom myxedema followed thyroid surgery, and our experience agrees with that of Baron,[14] who found a mean weight loss of 8.4 lb. with treatment in 58 female patients with myxedema. Dependent pitting edema in the absence of other manifestations of congestive heart failure was present in 30% of the cases.

Specific Laboratory Studies.—The most consistently abnormal specific laboratory test in this series was the protein-bound iodine determination. One or more determinations were available in 46 cases; all determinations were below 3μg. per 100 ml. of blood, except for one case in which a protein-bound iodine of over 25μg. % was obtained on two separate occasions. Since this patient was found to have a low radioiodine uptake, which did not respond to the administration of thyrotropin,* the patient was accepted as a true case of primary myxedema and the high protein-bound iodine attributed to an unidentified interfering substance.

Radioiodine uptakes were available in 49 cases. In 37 patients the uptake was below 10% in 24 hours, which is accepted as the lower limit of normal in the radioisotope laboratory of Georgetown University Hospital. In nine patients the radioiodine uptake was 10% to 12%, and in three patients with verified Hashimoto's struma the uptakes were 15%, 16%, and 56%. Normal or high uptake of radioiodine in Hashimoto's disease, despite unequivocal thyroid failure, has been mentioned by others.[15]

The serum cholesterol exceeded 290 mg. per 100 ml. in 64, or 86%, of the 76 cases in which it was determined prior to therapy. In 10 patients the cholesterol determination ranged from 250 to 290 mg. per 100 ml., and in only 2 cases was a value below 250 mg. per 100 ml. obtained. Despite the high frequency of abnormal serum cholesterol determinations in this series, caution must be used in evaluating the specificity of this test, since 11 of these patients had diabetes.

Basal metabolic rates were determined in 55 cases. Forty, or 73%, were below −20, and 16 of these were −35 or below. Ten patients had B. M. R.'s from −20 to 0, and 5 patients had B. M. R.'s from 0 to +10. The relatively high percentage (27%) of normal determinations reemphasizes the need for caution in interpreting even the properly performed basal metabolic rate test in myxedma suspects. Critical reviews of the basal metabolism test have appeared elsewhere.[16,17]

Miscellaneous Laboratory Tests.—That profound alteration in function of all organs and systems may occur in myxedema is generally accepted. In fact, abnormalities in cardiovascular, hematologic, neurologic, and renal function have been advocated as diagnostic adjuncts. Certain of these have been evaluated in the present series.

Electrocardiograms of 41 patients were reviewed. In 38, changes compatible with hypothyroidism—nonspecific T-wave changes, low voltage, bradycardia, or lack of somatic tremor [18]—were present. In two of these the diagnosis of myxedema was first suggested by the electrocardiogram. Conversely, there were two cases of classical myxedema in which initial electrocardiograms were considered normal. An additional case showed left bundle-branch block, presumably due to complicating coronary atherosclerosis.

It has been stated frequently that proteinuria may occur in myxedema in the absence of renal damage.[19-22] In this series, one or more urinalyses were available in 66 cases. Only 12 of our patients showed proteinuria. Of these, seven patients had either verified pyelonephritis or significant pyuria and one patient was in overt congestive heart failure. In only four patients could the proteinuria be attributed to the myxedema. Our findings support those of Beaumont and Robertson [23] and Roess and Levy.[24]

* Armour Laboratories, North Chicago.

Hematocrit measurements were available in 70 patients. In 6 of the 9 male patients the hematocrit was below 41%, while in 29 of 61 female patients an initial value below 37% was obtained. Since complete hematologic evaluation was lacking in most of the anemic patients, no attempt was made to determine which anemias were due solely to hypothyroidism.

Elevation of the sedimentation rate and subsequent return to normal after replacement therapy have been described in myxedema.[25] In 38 out of 55 of our patients the erythrocytic sedimentation rate was found initially to be greater than 20 mm. in one hour by the Wintrobe method. Unfortunately, follow-up in regard to this test was inadequate.

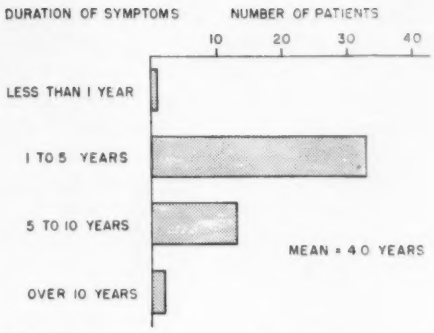
A summary of the pertinent specific and miscellaneous laboratory values is found in Table 4.

Delay in Diagnosis.—The date of onset of disease was estimated from available history in those patients in whom the diagnosis of myxedema was first established at this hospital. In the 49 cases of spontaneously arising myxedema (either idiopathic atrophy or those cases associated with goiter) in whom this estimate was possible, an average of 4 years, with a range of 8 weeks to 15 years, elapsed from the appearance of distinct symptomatology until the diagnosis was established. These data, charted in the Figure, agree closely with those of Means and Lerman.[8] As would be expected, prior

TABLE 4.—*Laboratory Tests*

	Normal Range	Cases, No.	No. Abnormal	% Abnormal
PBI	3.0-7.5 μg. %	46	45	98
RAI	10-40% in 24 hr.	49	37	76
Serum cholesterol	<290 mg. %	76	64	84
B. M. R.	−20-+10	55	40	73
ECG		41	38	93
Proteinuria		66	4 *	6
Hematocrit	Males>41% Females>37%	70	35	50
Sedimentation rate	<20 mm/hr.	55	38	69

* Only cases of unexplained proteinuria included.



Duration of symptoms prior to diagnosis in 49 cases of spontaneous myxedema.

thyroidectomy or ablation of the thyroid with radioactive iodine aroused earlier suspicion of myxedema, since in 19 comparable cases the average elapsed time from onset of symptoms until diagnosis of myxedema was only 1.4 years.

The reason for this striking delay was not failure to seek medical care. All patients had been seen by at least one physician during the period in which a diagnosis of myxedema could and should have been made. In extreme cases the patients had been under constant medical supervision by as many as five or six separate physicians over many years without suspicion of the true diagnosis. The most frequent erroneous diagnoses were congestive heart failure, arthritis or fibrositis, neuritis, refractory anemia, "functional" uterine bleeding, and "functional" or "psychogenic" disease.

The much rarer but all the more interesting complications of myxedema that were encountered in our series also emphasize the pleomorphic nature of this disease. In one patient with onset of myxedema at age 12, there was complete arrest of sexual maturation and failure of menarche, until treatment was instituted four years later. In a similar patient, who developed myxedema at age 11, normal menses were established at age 14. However, secondary sexual characteristics did not appear until replacement therapy was begun, at 17 years of age. One woman had undergone hysterectomy for menorrhagia, and an ad-

ditional four patients had uterine curettage before the true diagnosis was suspected. One patient was pregnant at term when the diagnosis was first established and spontaneously delivered a normal 7 lb. boy prior to initiation of thyroid therapy. Two patients in our series were psychotic; one had received electroconvulsive therapy during three years of institutionalization several years before the diagnosis was established. Complete disappearance of her paranoid psychosis followed thyroid therapy. There was no follow-up on the other patient. Severe abdominal pain was a dominant symptom in two patients, and still another underwent exploratory laparatomy because of clinical and radiologic evidence of intestinal obstruction. Both of these complications have been commented on in the literature.[26,27] In one patient, first-degree heart block, present initially, disappeared after thyroid therapy was started.

The frequency of coexistence of myxedema with diabetes mellitus [28,29] and with pernicious anemia [30,31] has been subjected to speculation. Most observers believe that there is little evidence for any more than chance concurrence. Our series contained 11 diabetics (1 of whom entered the hospital in moderate diabetic ketosis) and 2 patients with pernicious anemia.

Comment

The basic explanation for failure to recognize overt myxedema appears to stem from lack of comprehension of the diverse and often subtle manifestations of this disease. The patient who is suspected of thyroid dysfunction is often questioned and examined more in the light of what is expected to be heard or seen than in terms of what actually exists. Most of the "traditional" symptoms of myxedema are nonspecific and tend to occur so frequently in the general population that they are of little help in prompting consideration of the proper diagnosis. Other manifestations of potentially greater diagnostic specificity—deafness, tinnitus, dysarthria, marked weight gain, low blood pressure, or enlarged tongue—occur so infrequently or are so difficult to assess clinically that they seldom aid in diagnosis. In addition, it must be emphasized that a paucity of spontaneous complaints is a striking feature of some myxedematous subjects. Often it is only during treatment that such a patient becomes aware of how uncomfortable he really has been. Unfortunately, certain more prominent features of myxedema have had minimal emphasis. Several of these have served of great value to us in the clinical evaluation of the myxedema suspect.

To diagnose myxedema, one must think of it. As suggested above, the diagnosis is much more readily suspected in those cases with a known possible cause of myxedema, such as thyroidectomy, than in those cases in which the disease arises spontaneously. Consideration of the preceding data provides us with several additional aids to diagnosis. Foremost of these is an appreciation of the subtlety and polymorphism of the disease itself. In this day of specialization, the presenting or dominant symptom might lead the patient to consult first the dermatologist, the cardiologist, the rheumatologist, the hematologist, the neurologist, the otolaryngologist, or the gynecologist, each of whom must be prepared to make the diagnosis.

In the present series the most consistent complaint has been paresthesias of the hands and feet, often associated with myalgias and arthralgias. These may vary greatly in severity. Most frequently the patient complains merely that his hands and feet fall asleep easily. On the other hand, the discomfort may be so severe that the patient will sit on the edge of the bed for hours at a time whimpering and rubbing his hands and legs. Appearance of paresthesias shortly after thyroid replacement therapy has been started and awareness has improved may occur in those patients who did not notice the symptom initially or failed to mention it.

Every physician is familiar with the dull, apathetic, uncomprehending stare of the typical "myxedema facies." Unfortunately, in most cases, the appearance is not that characteristic. Change in physical appearance may be slight and so gradual in onset that not only the patient but close associates will mistake it for aging. Periorbital puffiness, the most constant physical feature in our series, should always suggest myxedema but may be difficult to recognize. In this regard, obtaining old and preferably serial photographs of the patient is indispensable in evaluating changes in appearance. Particularly helpful are informal family group snapshots which permit simultaneous evaluation of change in appearance with aging of brothers and sisters.

The pseudomyotonic or "hung-up" deep tendon reflex has been the commonest objective finding in the present series. In several patients chronically ill from other causes, myxedema was first suggested by the finding of these typical reflexes. In others, they have acted as confirmatory findings when there existed a paucity of other clinical features. An impression of myxedema in the absence of delayed relaxation phase of deep tendon reflexes must be held with some reservation. However, care must be taken in eliciting these reflexes, since in some patients inability to relax the limb completely leads to false prolongation of the delay phase. This difficulty can usually be eliminated by testing the Achilles reflex with the patient kneeling on the edge of a chair.

Throughout this paper the term "hypothyroidism" has been avoided whenever possible, for this term means different things to different people. To many, hypothyroidism is synonymous with myxedema, and all patients with true thyroid deficiency are considered to have the clinical entity, myxedema. In the opinion of others, there are patients with partial degrees of thyroid deficiency who do not exhibit true myxedema.[32] Even more confusing is the questionable entity of "idiopathic euthyroid hypometabolism," characterized by nonspecific complaints of lethargy, drowsiness, mental sluggishness, and weakness, by a "low" basal metabolic rate, and by the failure to respond to usual doses of desiccated thyroid and thyroxine.[33-35]

In all patients from this series on whom adequate follow-up information is available, there was satisfactory clinical response to replacement medication, usually desiccated thyroid, in eventual dosage of 1 to 3½ grains (0.065 to 0.26 gm.) given as a single dose daily. It is suggested that all cases of primary myxedema will respond similarly. Failure to respond to this regimen and initial lack of sensitivity to small doses of thyroid are taken as evidence of inaccurate diagnosis. If on reevaluation true thyroid deficiency is present, the possibility that one is dealing with hypopituitary myxedema should be considered. Such refractoriness may be overcome by the correction of the concomitant deficiency of the other target glands.

Summary

Despite progressively more accurate thyroid function tests, clear-cut clinical myxedema often goes unrecognized. Eighty cases of primary myxedema of various etiology have been reviewed in an attempt to formulate a systematic approach to this problem. The presenting complaints in myxedema are often nonspecific. However, the leading symptom in this series, paresthesias of the extremities, was of sufficient severity and frequency to be of considerable diagnostic import. The most frequent and probably most specific confirmatory sign was slow relaxation of the deep tendon reflexes.

Significant delay in diagnosis often occurs despite frequent medical consultation. Such oversight is abetted by the patient's inadequacy as a historian and by the examiner's preconceived and often erroneous concept of the clinical picture of myxedema. A history of prior thyroidectomy significantly reduces the delay in diagnosis.

The most helpful laboratory test in this series was the protein-bound iodine deter-

mination, which was abnormal in 98% of cases. Adequate response to desiccated thyroid is a characteristic of true primary myxedema. Failure of response should suggest inaccurate diagnosis.

It appears that despite increased understanding of thyroid disease and development of more precise tests of thyroid function, thyroid deficiency is being overlooked with the same frequency as was the case a quarter century ago.

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Hemodynamic Effects of Isoproterenol in Complete Heart Block

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The use of isoproterenol in patients with complete heart block has become an important part of the therapeutic armamentarium. Although Kaufman et al.,[1] utilizing the ballistocardiograph, have studied the circulatory effects of this drug in normal subjects, there has been only one report concerning the hemodynamic effects of isoproterenol in patients with heart block.[2] It was thought that further information concerning the effect of this drug in patients with heart block would be of interest.

Methods and Materials

Six patients with complete heart block and one with 2:1 heart block were studied. These patients varied in age from 15 to 77 years, and six were males. The etiology of the heart block was considered congenital in one patient (Patient 1) and obscure in two patients (Patients 2 and 7), and in the remainder the block was thought to be on the basis of arteriosclerotic heart disease (Table 1). In addition, five convalescent patients with no apparent cardiovascular abnormality were also studied. This control group included four men and one woman, ranging in age from 28 to 66 years.

All subjects were studied in the fasting state without sedation. Cardiac output was determined by the dye-dilution technique. Evans blue dye (T-1824) was injected from a marked syringe through a Cournand catheter into the right atrium or superior vena cava. Arterial samples were obtained from the brachial artery and drawn by a constant suction device[3] through a cuvette densitometer, as described by Shadle and co-workers.[4] The dye concentration was recorded on a Hathaway photographic recorder. The catheter and marked syringe were calibrated with saline and plasma, the plasma flow being converted to whole-blood flow by means of the hematocrit. No correction for trapped plasma was made. This method of calibrating the cuvette densitometer for determination of cardiac output is valid in the presence of normal or near-normal blood arterial oxygen saturation.[5] While the arterial oxygen saturation was not determined in this study, there was no reason to believe that any of the patients had a gross decrease in saturation or a variation in arterial oxygen saturation during the period of study. Pressures were obtained with Sanborn electromanometers and recorded on a Sanborn Polyviso.

After control observations were completed, 10-20 mg. of isoproterenol was given sublingually to all patients except the one with 2:1 heart block (Patient 7). The latter received 0.2 mg. subcutaneously. In the case of the patients with heart block, observations were repeated 21 to 52 minutes after administration of the drug. In the control group, multiple studies were performed from 27 to 122 minutes after the drug was given. In the patient given isoproterenol subcutaneously, repeat studies were done 21 minutes after the drug was given.

The work of the left ventricle against pressure was expressed in kilogram-meters per minute; stroke work was expressed as gram-meters per minute, and total peripheral resistance, in dynes-seconds/cm.$^{-5}$

Results

The results are indicated in Tables 1 and 2 and in Figures 1 to 4. The resting cardiac index in the heart block group varied from 1.24 to 3.22 liters per minute per square meter of BSA (body surface area), averaging 2.45 liters. Four patients in this group had a cardiac index below 3.0 liters by this method. All showed a rise in cardiac index after isoproterenol was given, the index varying from 2.13 to 5.16 liters and averaging 3.58 liters. The percentage rise varied from 10.2% to 71.7% and averaged 49.1% (Fig. 1). Three of the four patients with

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TABLE 1.—*Hemodynamic Effects of Isoproterenol in Heart Block* *

Patient	Age	Sex	Dose, Mg.	Interval, Min.	CO, L/Min.	CI, L/Min /M.²	VR	SO, Cc/ Stroke	SI, Cc/Stroke /M.²	BA, Mm. Hg S	BA, Mm. Hg D	BA, Mm. Hg M	RA, Mm. Hg	LVW, Kg.-M /Min.	LVSW, Gm. M/Min.	TPR, Dynes-Sec./Cm.⁻⁵
1	28	F	20	Before	4.77	3.22	49	97.3	65.7	96	42	65	5	4.2	86.0	1,089
				27 After	7.63	5.16	59	129.3	87.4	102	56	79	5	8.2	138.9	828
2	15	M	10	Before	3.16	2.55	34	92.9	74.9	147	58	109	4	4.7	137.7	2,757
				26 after	3.49	2.81	37	94.3	76.0	153	41	77	5	3.7	98.8	1,763
3	42	M	15	Before	5.02	2.99	43	116.7	69.5	116	49	67		4.6	106.3	1,067
				34 after	6.22	3.70	49	126.9	75.5	134	69	92		7.8	158.8	1,182
4	44	M	20	Before	5.89	3.10	48	122.7	64.6	109	40	62		5.0	103.5	841
				52 after	9.44	5.00	52	181.5	95.9	118	43	77		9.9	190.0	647
5	77	M	20	Before	2.32	1.24	32	72.5	38.9	250	72	117	7	3.7	115.4	4,030
				39 after	3.97	2.13	38	104.4	56.1	257	64	117	9	6.3	166.1	2,355
6	54	M	20	Before	2.57	1.36	37	69.5	36.7	138	80	99	8	3.5	93.6	3,079
				35 after	4.31	2.28	40	107.7	57.0	154	70	95	8	5.6	139.2	1,762
7 †	36	M	0.2	Before	5.79	2.68	48	120.6	56.9	118	62	77	15	6.1	126.3	1,063
				21 after	8.60	4.00	80	107.5	50.0	119	62	76	9	8.9	111.1	700

* CO indicates cardiac putput; CI, cardiac index; VR, ventricular rate; SO, stroke output; SI, stroke index; BA, brachial arterial pressure; RA, right atrial pressure; LVW, left ventricular work; LVSW, left ventricular stroke work; TPR, total peripheral resistance; S, systolic; D, diastolic; M, mean.

† 2:1 heart block, subcutaneous injection.

TABLE 2.—*Hemodynamic Effects of Isoproterenol in Control Subjects* *

Patient	Age	Sex	Dose, Mg.	Interval, Min.	CO, L/Min.	CI, L/Min /M.²	VR	SO, Cc/ Stroke	SI, Cc/Stroke /M.²	BA, Mm. Hg S	BA, Mm. Hg D	BA, Mm. Hg M	RA, Mm. Hg	LVW, Kg.-M /Min.	LVSW, Gm. M/Min.	TPR, Dynes-Sec./Cm.⁻⁵
8	64	M	20	Before	5.11	2.43	75	68.1	32.4	142	78	99	6	6.9	91.7	1,548
				29 after	8.12	3.87	70	116.0	55.2	139	74	95	5	10.5	149.9	935
9	28	M	10	Before	10.88	6.08	80	122.2	68.2	150	88	116	7	17.2	192.7	852
				30 after	13.77	7.69	89	154.6	86.3	144	75	93	6	17.4	195.5	539
10	66	M	20	Before	5.42	3.38	70	77.1	48.2	164	81	115	5	8.4	120.6	1,605
				27 after	7.10	4.44	96	74.0	46.2	182	84	110	8	10.6	110.7	1,238
11	36	F	20	Before	6.50	4.14	110	59.1	31.2	135	85	97	5	8.6	78.0	1,192
				33 after	11.78	7.50	142	82.9	52.8	140	80	104	4	16.7	117.3	705
12	47	M	15	Before	5.82	3.06	84	69.3	36.5	118	73	102	5	8.1	96.1	1,401
				31 after	6.73	3.54	100	67.3	35.4	120	75	100	5	9.2	91.5	1,187

* For explanation of abbreviations see footnote to Table 1.

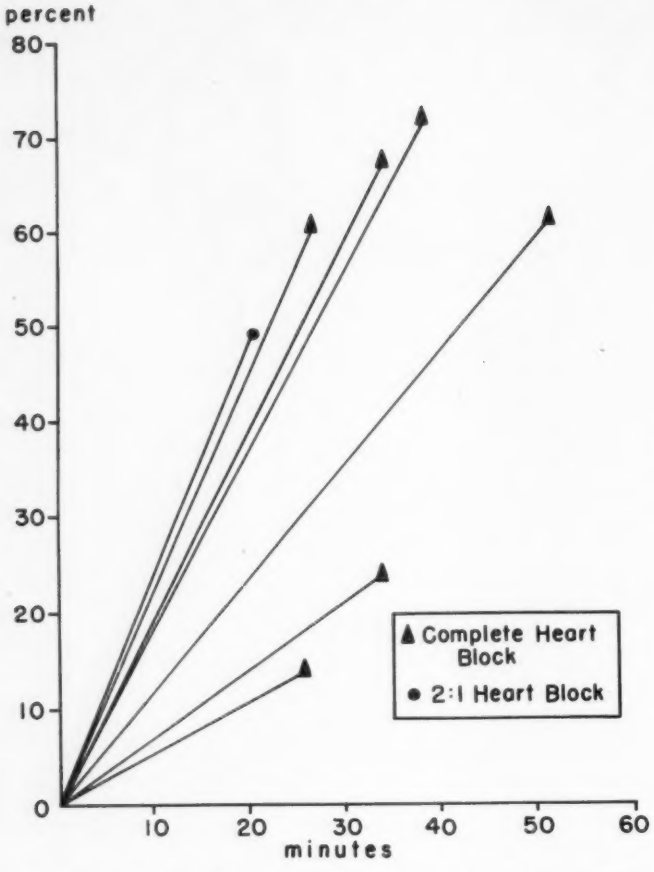

Fig. 1.—Per cent change in cardiac index with isoproterenol in heart block.

a resting cardiac index below 3.0 liters still had an index below this figure after the drug, despite a significant rise in output. Among the six patients with complete heart block, the resting ventricular rate averaged 40.7 beats per minute prior to isoproterenol and 45.8 beats per minute after. The rate increased in all patients, the range of increase being from 3 to 10 beats per minute. The patient with 2:1 block, who received the subcutaneous injection, developed a supraventricular tachycardia with a peak rate of 130 beats per minute. Post-drug studies were done on this patient when he had a supraventricular rhythm, probably nodal, at a rate of 80 per minute.

The stroke volume in the heart block group averaged 98.9 cc. per stroke, varying from 69.5 cc. to 122.7 cc. per stroke. Three patients had less than a 10% rise in stroke volume after the drug (Fig. 2). Included among the three is the patient given the subcutaneous injection who developed the supraventricular tachycardia.

In the small number of heart block patients in this series there was no correlation between heart rate and either cardiac index or stroke volume in the control period. However, the ages of the patients and etiologies of their heart block varied considerably.

In the heart block group brachial artery and right atrial pressures showed relatively little change. Although the brachial artery systolic pressure rose in all cases, the average rise was only 10 mm. Hg. Arterial diastolic

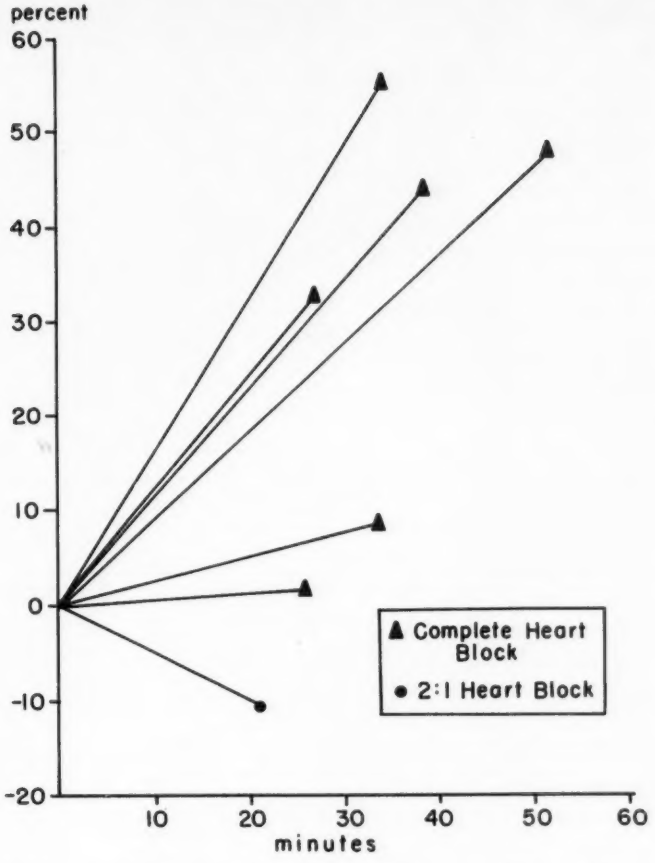

Fig. 2—Per cent change in stroke volume with isoproterenol in heart block.

pressure varied only slightly and inconstantly. The peripheral resistance fell in all but one patient. Right atrial pressure remained essentially unchanged except for the patient with the supraventricular tachycardia, in whom it fell from 15 to 9 mm. Hg.

The left ventricular work rose in all heart-block patients except one (Patient 2). This latter patient was a 15-year-old boy, given the smallest sublingual dose in the group, 10 mg. The mean left ventricular work averaged 4.52 kg.-meters per minute and rose after the drug to an average of 7.19 kg.-meters per minute. The stroke work also fell in the case that had had a fall in left ventricular work (Patient 2), and in addition, the patient who received parenteral isoproterenol and developed the tachycardia had a fall in stroke work. The remaining heart block patients demonstrated a rise in left ventricular stroke work.

Although multiple studies were obtained in some of the normal patients for as long as two hours after sublingual administration, the results illustrated in Table 2 are those obtained closest to one-half hour after the drug was administered, in order that they might be comparable to the results obtained in the heart-block patients.

Figures 3 and 4 illustrate the results of multiple determinations of cardiac index and stroke volume in the control group. It would appear that among these patients the maximum effect is obtained within 40 minutes after the administration of 10 to 20 mg. of isoproterenol sublingually.

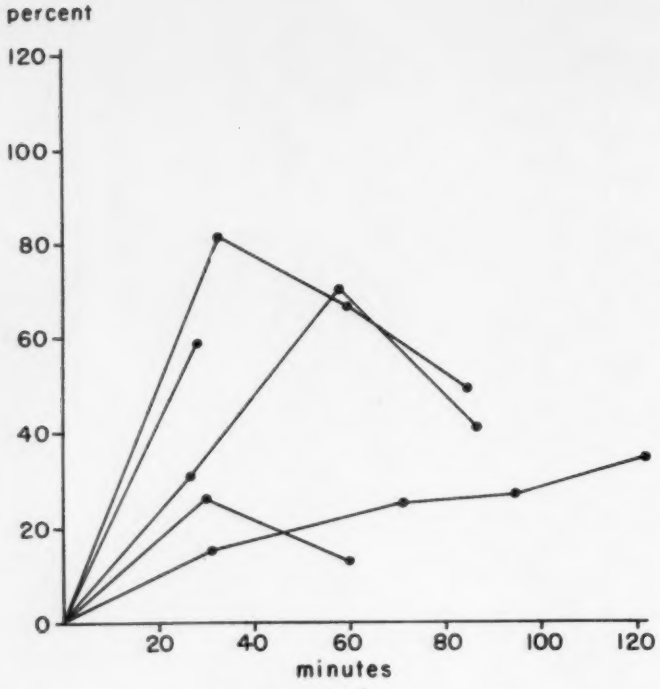

Fig. 3.—Per cent change in cardiac index in control subjects with isoproterenol.

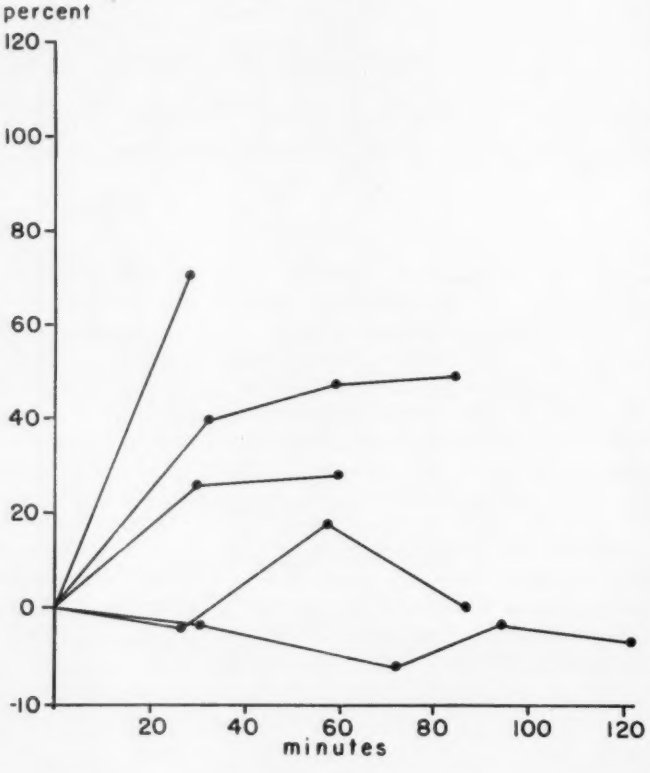

Fig. 4—Per cent change in stroke volume in control subjects with isoproterenol.

The mean resting cardiac index in the control group was 3.82 liters per square meter of BSA, varying from a below-normal value of 2.43 (Patient 8) to an above-normal value of 6.08 liters (Patient 9). After the drug, the cardiac index varied from 3.54 to 7.69 and averaged 5.41 liters. All patients increased their cardiac index, the mean percentage rise being 42.7% and the range of increase 15.4% to 81.1% (Fig. 3). The minute ventricular rate increased in all but one patient (Patient 8), who had a decrease in ventricular rate from 75 to 50. In general, the increase in heart rate in this control group was greater than in the heart-block group. The four patients in regular sinus rhythm who increased their heart rate had increases of 9, 26, 32, and 16 beats per minute.

The stroke output increased in three of five control patients (Fig. 4). Two patients (Patients 10 and 12) had a slight and probably insignificant drop in stroke output. The control mean stroke volume was 79.2 cc. per stroke, and it rose after sublingual isoproterenol to 99.0 cc. per stroke. In this small series there was no correlation between change in rate after isoproterenol and change in stroke volume. Thus, it would appear that the effect of this drug was similar in the control and in the heart block group in causing an increase in cardiac index but an inconsistent increase in stroke volume.

There was no consistent effect on either brachial artery systolic or diastolic pressure or right atrial pressure. As in the heart-block group, after the drug there tended to be a fall in total peripheral resistance.

The left ventricular work against pressure rose in four of five patients, while in one patient the left ventricular work showed no change. The mean left ventricular work before and after isoproterenol was 9.81 and 12.87 kg.-meters per minute, respectively. The left ventricular stroke work rose in only two patients in the control group, showed no significant change in two patients, and fell in one patient. The pre- and post-isoproterenol left ventricular stroke work averaged 115.80 and 132.97 gm.-meter per minute, respectively.

Comment

Isoproterenol is a most potent drug in the prevention and treatment of ventricular arrest in complete heart block.[6-9] The positive chronotropic effect of this drug has also been demonstrated in dogs with complete heart block [10] and in the rabbit heart.[11] In cats it does not dispose to ventricular fibrillation,[12] and it is one of the most effective sympathomimetic amines in lowering the irritability threshold while producing the least change in automaticity.[13]

In dogs there has been found a marked increase in contractile force following isoproterenol administration.[14,15] The drug has been shown to increase the coronary flow in dogs [16] and rabbits [17] and to intensify the dog's myocardial oxygen consumption to a much greater extent than epinephrine.[16]

From our data it appears that sublingual isoproterenol has both an inotropic and chronotropic effect in normal and heart block patients. Increases in ventricular rate were observed in both groups but were more marked in the control patients, who had increases of their sinus rates from 9 to 32 beats per minute. The increases in rate in the patients with heart block were less striking, and the average increase was 5 beats per minute. The greater effect of isoproterenol on the sinus mechanism, as compared to a nodal or ventricular focus, has been found by Zoll et al.[9]

All heart-block patients and control subjects increased their cardiac output after this drug. This increase in output in both the heart block and the control patients was inconsistently accompanied by an increase in stroke volume. The left ventricular work and stroke work in most of the heart block patients rose markedly after this drug. These results for sublingual administration of the drug are in agreement with the recently published studies of Stack et al.[2] The latter authors found similar hemodynamic effects when isoproterenol was administered intravenously and sublingually.

It is not known if isoproterenol produces a change in myocardial efficiency in the human. Recently Dodge and Murdaugh [18] have given the drug to subjects with heart failure. In their acute experiment they demonstrated an increase in cardiac output and urine flow and did not observe any untoward effects.

Summary

Isoproterenol was given sublingually to six patients with complete heart block and to five control subjects. Both groups demonstrated an increase in cardiac output. In most there was an increase in stroke output and a decrease in total peripheral resistance. The ventricular work was increased in the heart block cases and variably affected in the controls. A case of 2:1 heart block who developed a supraventricular tachycardia after subcutaneous injection is cited.

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Armchair Treatment of Myocardial Infarction

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Recently there has been considerable interest in the armchair treatment of myocardial infarction. Clinical observations of Levine [1] indicated that patients generally did better when they were allowed to sit up in a chair at intervals during the day than they did at complete bed rest. Improvement was striking in some of the patients who were desperately ill with congestive heart failure. It was stressed that this regimen improved the psychological state of the patient and facilitated the rehabilitation process.[2] They could find no evidence that the armchair treatment produced any deleterious long-range effect.[3]

Clinical observations were made by Beckwith et al.[4] in a series of 80 patients with acute myocardial infarction, one-half of whom were kept at complete bed rest and the other half allowed to sit up in a chair at intervals during the day. The mortality rate was no higher among the latter half than among the former.

Coe [5] has shown by catheterization studies that cardiac work in both normal persons and patients with arteriosclerotic heart disease is less when they are sitting in a chair than when they are in the supine position.

The present study was devised to evaluate further (the concept of) the "Armchair Treatment," by determining, through utilization of Starr's cardiac work principle, the cardiac work of patients who were convalescing from acute myocardial infarction while sitting in a chair and lying in bed, respectively.

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Methods and Materials

Sixteen patients with acute myocardial infarction were studied, and cardiac work determinations were made at intervals after onset during their three-week hospital stay. Between the first and sixth days after the onset of the infarction, patients were allowed to sit up in a chair one-half hour twice daily for three days and then one hour twice daily for three days. This was increased gradually until they were allowed to sit up ad lib. No patients were urged to sit up beyond the point of fatigue. As a rule, the patients were first permitted to sit up on the side of the bed and to swing their legs, to see how they tolerated and adjusted to the sitting position. No patients who had shock or pain at the time of the study were allowed to sit up. Ambulation was not allowed at any time during the three weeks.

Blood pressure and pulse rate were determined at 5-minute intervals for 20 minutes in both lying and sitting positions. Average figures for systolic and diastolic pressures were used in determining the cardiac work in supine and sitting positions. Cardiac work (work of the left ventricle) was determined by use of Isaac Starr's cardiac work formula,* which employs stroke volume, resistance (mean blood pressure), and a constant.[6,7]

After the left ventricular work per beat is estimated, the result is multiplied by the heart rate per minute, which is the cardiac work per minute. In 13 controls, cardiac work determinations were made.

Because of inability to estimate stroke volume by the Starr formula in patients with arrhythmias,

* Cardiac work, in gram-meters $= -1.67 - 0.0113\ X_e\ Y_e$

X_e (stroke volume) in cc. $= 101 + 0.5$ pulse pressure (auscultation mm. Hg) $- 0.59$ diastolic (auscultation at disappearance of sounds, mm. Hg) $- 0.61$ age in years

Y_e (mean pressure) in mm. Hg $= 3.21 + 0.5$ systolic pressure (auscultation mm. Hg) $+ 0.52$ diastolic pressure (auscultation at disappearance of sounds, mm. Hg)

TABLE 1.—*Thirteen Normal Controls*

Stroke Volume, Cc.		Cardiac Output, Cc/Min.		Cardiac Work, Gm/M/Min.		Average Blood Pressure, Mm. Hg		Average Heart Rate/Min.		
Down	Up	Down	Up	Down	Up	Down	Up	Down	Up	Age
33.6	27.05	3,359	2,705	3,860	3,207	114/80	114/86	100	100	61
30.0	26.8	3,305	2,973	4,024	3,517	120/86	120/89	110	111	61
51.6	33.4	3,094.8	2,138	4,513.8	2,822	139/80	131/93	60	64	52
42.6	41.1	2,639	2,469	3,478	2,892	129/82	124/81	62	60	55
42.1	35.4	2,273	2,336	2,889	2,858	132/90	123/92	54	66	44
47.8	31.3	2,984	2,222	3,863	3,089	139/88	141/104	62	71	44
41.4	37.4	3,519	3,142	4,548	4,242	142/84	147/90	85	84	64
46.6	39.3	3,868	3,223	5,069	4,485	148/82	153/91	83	82	64
27.5	43.7	3,087	3,103	3,121	3,238	103/73	106/76	68	71	45
49.3	41.3	3,845	3,180	3,783	3,457	102/69	110/80	78	77	45
47.5	46.5	3,040	3,162	3,424	3,522	118/78	116/78	64	68	45
52.8	42.8	3,802	3,082	5,306	4,262	162/81	155/87	72	72	67
59.0	52.9	4,602	3,968	6,591	5,895	170/79	173/86	78	75	67
Mean * —5.7		—439.5		—540		+2.6		+2		—

* + indicates increase in armchair position; —, decrease in armchair position.

no patients were included who did not have normal sinus rhythm.

Results

In 11 of 13 controls (Table 1) in the sitting position, the cardiac work was found to be less, ranging from 2% to 38% and averaging 12.9% less than in the reclining position. In two controls the cardiac work averaged 3% higher in the sitting position.

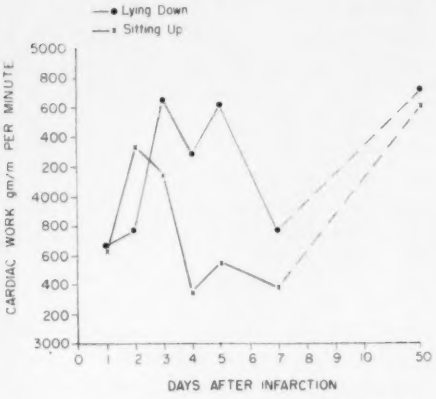
Cardiac work was found to be less in 14 of 16 patients in the sitting position (Table 2). Cardiac work ranged from 1% to 35% and averaged 14.5% less in the sitting position than in the reclining position. In two patients the cardiac work averaged 2.5% higher in the armchair position.

For the control group, the mean difference in cardiac work between the armchair and lying positions was 572 gm. per meter, and the standard error of this difference was 141.4. For the patients the mean difference between the two positions was 437 gm. per meter and the standard error 120.5. The reduction in cardiac work when the patient is sitting up is statistically significant

TABLE 2.—*Sixteen Patients*

Patient	Stroke Volume, Cc.		Cardiac Output, Cc/Min.		Cardiac Work Gm/M/Min.		Average Blood Pressure, Mm. Hg		Average Heart Rate		Age	No. of Observations
	Down	Up	Down	Up	Down	Up	Down	Up	Down	Up		
1	50.2	50.0	3,416	3,359	3,949	3,629	127/74	123/72	68	66	55	5
2	47.8	46.5	2,545	2,840	3,489	3,554	129/80	138/83	60	61	54	10
3	41.0	33.0	3,680	3,288	4,215	3,862	121/75	123/83	91	100	63	7
4	27.9	18.0	2,009	1,232	2,909	1,861	161/107	157/113	68	69	58	4
5	45.9	39.7	2,793	2,752	3,097	2,751	119/74	104/72	61	70	56	2
6	35.7	38.3	2,249	2,183	2,438	2,200	116/75	108/69	63	57	68	1
7	48.0	44.3	2,928	2,968	3,081	3,149	109/74	108/77	61	67	44	1
8	29.2	27.7	2,132	2,022	2,964	2,774	148/98	145/98	73	73	64	1
9	44.8	36.5	3,315	2,811	4,344	3,550	150/79	140/82	74	77	74	1
10	32.9	31.3	2,796	2,723	3,120	2,038	116/81	115/82	85	87	62	1
11	44.6	41.6	3,570	3,410	3,724	3,441	105/77	99/77	80	82	41	1
12	38.7	36.0	3,096	3,168	3,736	3,406	121/83	109/80	80	88	53	1
13	47.5	40.5	3,800	3,564	4,016	3,846	109/75	109/81	80	88	43	1
14	57.2	53.0	4,118	4,028	5,522	4,294	154/79	127/71	72	76	57	1
15	47.8	38.4	3,202	2,761	3,330	2,664	108/67	98/71	67	72	56	1
16	28.8	25.4	1,840	1,651	2,202	2,035	126/87	129/91	65	65	67	1
Mean *	—4.1		—170.5		—520		—2.5		+3			

* + indicates increase in armchair position; —, decrease in armchair position.



Daily cardiac work of Patient 3 in reclining and armchair positions.

because the probability is less than 0.01 in both the patient and the control group.

It can be seen in Tables 1 and 2 that when the controls and the patients assume the armchair position there is usually only a slight increase in heart rate. The stroke volume in both groups was less in the armchair position with the exception of two cases, one in the control group and one in the patient group. The mean blood pressure changed very little with the person in the sitting position.

None of the patients experienced chest pain, dyspnea, or anxiety when they sat up. Only two patients had initial dizziness when they first sat up, but this was transient and did not occur on subsequent occasions.

An example of daily cardiac work is shown in the Figure. Patient 3, a 63-year-old white man, was admitted to the hospital on April 18, 1955, with severe chest pain. He showed unequivocal clinical evidence of myocardial infarction, including electrocardiographic changes. There was no shock, congestive failure, or arrhythmia. Anticoagulation was carried out. As outlined above, at the beginning of the first hospital day the patient began to sit up in the chair, and the cardiac work was determined in both supine and sitting positions. The graph indicates that, with the exception of the second day, the cardiac work was less in the sitting position.

Comment

In the past, several clinical observations have been made in myocardial infarction. However, little direct study has been made of hemodynamic changes accompanying acute myocardial infarction in man because of the difficulties involved in acutely ill patients. Consequently, in cardiac work estimation we have used Starr's cardiac work equation, which involves no discomfort or anxiety to the patient and which we have found easy to employ. Starr has shown that in two-thirds of the estimates of stroke volume with his equation the error was less than 5.9 ml. Also, with use of the disappearance of sounds by auscultation for diastolic pressure reading, the error is further minimized. An inspection of our results reveals that our values compare very closely with Starr's predicted cardiac work values. An examination of the individual heart rate, pulse pressure, and blood pressure figures would seem to indicate that both normal controls and patients adjust in a normal fashion to the upright position and that cardiac work as estimated is less, with the exception of two patients in whom the difference was only 2.5%.

The effect of the armchair position on the cardiovascular and respiratory systems was studied by Coe. Using the dye-injection method with cardiac catheterization in order to determine the cardiac output and cardiac work, he studied three patients with normal cardiovascular systems and three with arteriosclerotic heart disease. In four of the six patients there was a diminution in the calculated pulmonary blood volume when a patient assumed the armchair position—in one of them by as much as 685 cc. with prompt relief of dyspnea. The mean reduction of the cardiac work in the sitting position was 23% in six patients.

Perera and Berliner [8] earlier showed that hemodilution and a decrease of serum protein occurred in the supine position with an increase in plasma volume. They pointed out that the close correlation between nocturnal hemodilution and attacks of paroxysmal dyspnea suggests that an increase in plasma volume is an important factor in the production of acute left ventricular fail-

ure in persons with organic heart disease. McMichael and McGibbon[9] have also shown that the recumbent position produced an increase in pulmonary blood volume. Thompson et al.[10] showed that during quiet standing the decrease in total plasma volume reached about 11%. These observations indicate that the supine position, even though not directly compared with the armchair position, may produce effects on the cardiovascular and respiratory systems. These effects may well be aggravated where there is a damaged heart.

So far, we have found no specific information on the effect of the armchair position on the coronary blood flow. However, Coe points out that mainly aortic pressure determines the pressure head applied at the coronary orifices. In his study, he found very slight changes in the arterial pressure when the patients assumed an armchair position. He expressed the opinion that coronary blood flow was not decreased in this position, since decreased back-pressure in the armchair position may even lead to increased coronary flow as long as there is no postural hypotension.

Serial daily serum glutamic oxalacetic transaminase (SGOT) studies were done in a number of these and in some other patients with myocardial infarction. From these observations it was evident that the armchair position did not result in any increased activity of the SGOT level in the serum. These observations will be published later.

Summary

Cardiac work was determined by the Starr method in 16 patients in the supine and sitting positions after an acute myocardial infarction. With the exception of two patients, cardiac work was less in the armchair position. The mean reduction of the cardiac work was 14.5%.

These studies appear to support the view that the armchair treatment is a safe and advantageous method of handling patients with acute myocardial infarction.

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Treatment of Pneumococcic Meningitis

Results When Penicillin Was Used Alone Compared With Those When Penicillin and Streptomycin Were Used Together, With and Without Hydrocortisone: Alternate Patient Studies

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The results of treatment of patients with pneumococcic meningitis have varied widely.[1-21] While some of the variations may be attributed to the choice of treatment, particularly with antibacterial agents, the magnitude of differences has been as great between different clinics using the same regimen as between different regimens in the same clinic. Several factors, such as the quality of supportive treatment and availability of nursing services, may influence results, but the nature of the patient being treated appears to be of primary importance. This is emphasized by analysis of the difference in results in various age groups and of the complicating diseases and the acuity of the illness among those patients who die as compared with those who recover.

The effect of factors of selection of patients entering a hospital on prognosis made the study of this disease by alternate case method seem necessary. Because of the fact that rapidity of action should be desirable in pneumococcic meningitis, in which death occurs in many cases within a few hours or one to two days, it was thought that a combination of rapidly bactericidal drugs, such as streptomycin and penicillin, might be more effective than penicillin alone. The efficacy of this combination of drugs in endocarditis caused by α-hemolytic streptococci furthered this hope. Moreover, because the course of patients with pneumococcal meningitis suggested early and marked irreversible tissue damage, we began, in 1950, to use the adrenal corticosteroids in an attempt to reduce this damage and thereby preserve life and function until the antibiotics had an opportunity to work. As previously reported,[22] however, the use of these agents in patients who were considered to be in a critical condition was not rewarding, and in 1955, it was decided that earlier use might give better results. For this reason, beginning at that time, a separate alternation of patients was begun, in which there was an attempt to estimate the worth of hydrocortisone.

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Presented in part at meeting of the Midwestern Section, American College of Physicians, Milwaukee, 1958.

From the Department of Preventive Medicine, University of Illinois, and the Municipal Contagious Disease Hospital.

Method

All patients were treated on the wards of the Municipal Contagious Disease Hospital of Chicago. In this institution every attempt was made to start treatment as promptly as possible. In almost all patients, this was accomplished by the complete work-up in the admitting suite, where the history and physical examination were done and a lumbar puncture performed when meningitis was suspected. The fluid was examined immediately for bacteria, and if Diplococcus pneumoniae (pneumococci) were seen the patient was placed in one of the two antibiotic groups. If no D. pneumoniae or other organisms were seen but the spinal fluid appeared to be that of a purulent meningitis and the patient was more than six years old, he was placed in the appropriate group on the presumptive diagnosis of pneumococcal meningitis. Hence, these latter patients, in whom the etiologic diagnosis could not be made by examination of an initial stained smear of the spinal fluid, were alternated separately, and when the subsequent cultures established a pneumococcal etiology they were included in this series. On the other hand, when such patients were six years old or less they

TABLE 1.—*Data on Patients Omitted from Alternate Case Study*

Patient	Age, Yr.	Comment
1	1 6/12	Died on admission before treatment could be started; artificial respiration only
2	38	Died on admission before treatment could be started; with ruptured mycotic aneurysm of circle of Willis & pneumococcic endocarditis; artificial respiration only
3	2/12	Missed diagnosis; smear interpreted as H. influenzae; treated with chloramphenicol; died within 18 hr.; postmortem cultures positive for D. pneumoniae
4	7/12	CSF smear negative; culture positive for D. pneumoniae on 3d day; treated 3 days with tetracycline, then penicillin; recovered
5	5/12	Missed diagnosis; original culture considered to be H. influenzae; treated with chlortetracycline; died in 54 hr.
6	4/12	Treated with 10 antibiotics singly & in combination for 12 days in another hospital before transfer; died in 10 hr.; unsuited for series

were treated as if they had Hemophilus influenzae meningitis and consequently were not included in this study, except as considered below and in Table 1. This initial diagnostic study usually required from 15 to 30 minutes. While it was being finished an indwelling plastic tube was inserted into an appropriate vein and fluids and other supportive medication, as indicated, were started. As soon as the therapeutic group could be assigned, intravenous drug therapy was started and the patient, transported to the ward. The drug regimens used were as follows:

1. *Penicillin Group.*—Potassium penicillin G, 10,000,000 units daily as a continuous intravenous drip, was given to children under 12, and 24,000,000 units daily, to older children and adults. On the fifth day if the patient was doing well or at any later day in the patient who responded more slowly, 600,000 units of procaine penicillin in aqueous suspension was given at six-hour intervals. On the next day the latter drug was continued and the intravenous medication discontinued. The patient was treated for at least seven days after the temperature had permanently fallen below 101 F rectally.

2. *Penicillin-Streptomycin Group.* — Penicillin, used as above, plus streptomycin, was given intramuscularly four times daily in a dose of 12.5 mg. per kilogram, with a maximum dose of 3 gm. daily in adults. At the end of the five days this dose was reduced to 25 mg. per kilogram in children and 2 gm. daily in adults, and if the drug was needed after the 10th day, the adult dose was lowered to 1 gm. daily. Streptomycin was always discontinued by the 15th day.

3. *Steroid Group.*—In the last half of the study, alternate patients in each of the above drug groups received hydrocortisone in addition to the appropriate antibiotics. This drug was administered continuously intravenously for several days, in a dose of 250 mg. every 24 hours in adults and older children and 4.0 mg. per kilogram every 24 hours in the younger patient. Hydrocortisone was always given for five days, but in the patient who was doing well it was administered intravenously for only 48-72 hours. In many patients, however, the intravenous route was used for the entire five days. On the sixth and seventh day, corticotropin (ACTH) was given intramuscularly, 100 mg. per day in adults and 1 mg. per kilogram per day in children.

That the patients were kept in the proper therapeutic group has been verified by the fact that the serial hospital admission numbers revealed no patient who was improperly treated. Since all patients admitted to this hospital were treated by the same physicians, it is possible to state exactly the number of patients who were omitted from the alternate case study and the reason for this action. A summary of these patients is given in Table 1. Since about 90% of the patients who die in this hospital are examined at autopsy, it is unlikely that there were other patients not appropriately treated. According to the chart number, if it had been possible to place the patients in our series, those numbering 1, 3, 4, and 6 would have received the combination of drugs and No. 2 and 5, penicillin only.

Symptomatic treatment was carried out as necessary. Particular attention was paid to maintenance of an adequate airway, which in several patients required tracheotomy. In addition, shock occurred in 10 patients, for which levarterenol ([*l*-norepinephrine] Levophed) was given. Blood was given to patients with marked anemia or acute blood loss caused by gastric hemorrhage. Almost all of the patients requiring these measures failed to recover. Indwelling catheters were avoided as much as possible, and in the patients who were vomiting excessively parenteral feeding was used. Otherwise the patient was tube fed, if uncooperative, or was allowed to eat. Before the alternation of steroid hormones was begun, these hormones were used on five patients who were in critical condition.

Tables 2, 3, and 4 illustrate the data which indicated the degree of comparability of the two groups. It can be seen that there were insignificant differences in the age distribution, the duration of illness before treatment was started, and the cerebrospinal fluid findings between the two groups.

TABLE 2.—*Ages of Patients With Pneumococcic Meningitis*

Age, Yr.	Treatment Group: Penicillin Alone — Patients, No.	Penicillin Alone — Died	Penicillin Alone — Duration of Therapy Before Death	Penicillin + Streptomycin — Patients, No.	Penicillin + Streptomycin — Died	Penicillin + Streptomycin — Duration of Therapy Before Death, Hr.	Total — Patients, No.	Total — Died
0-¼	4	0		4	1	24	8	1
>¼-½	1	0		1	1	12	2	1
>½-1	5	0		3	0		8	0
>1-2	3	0		5	0		8	0
>2-20	14	0		8	2	24+48	22	2
21-50	4	0		7	1	48	11	1
>50	6	2	72 hr. + 7 days	3	0		9	2
Total	37	2		31	5		68	7

TABLE 3.—*Duration of Illness Before Treatment of Patients with Pneumococcic Meningitis*

Days Before Treatment	Treatment: Penicillin Alone — Patients, No.	Penicillin Alone — Died, No.	Penicillin + Streptomycin — Patients, No.	Penicillin + Streptomycin — Died, No.	Total — Patients, No.	Total — Died, No.
<1	6	0	60	2	12	2
1-2	9	0	4	12	13	1
2-3	7	0	6	0	13	0
3-4	3	1	1	0	4	1
4-5	3	0	2	0	5	0
5 or more	9	1	12	2	21	3

TABLE 4.—*Cerebrospinal Fluid, Cell Count, and Protein and Sugar Concentration Before and After Treatment*

Day of Treatment Specimen Obtained	Treatment: Penicillin Only — Cell Count Cu. Mm. ±SE	Penicillin Only — Protein, Mg/100 Ml. ±SE	Penicillin Only — Sugar, Mg/100 Ml. ±SE	Penicillin + Streptomycin — Cell Count/ Cu. Mm. ±SE	Penicillin + Streptomycin — Protein, Mg/100 Ml. ±SE	Penicillin + Streptomycin — Sugar, Mg/100 Ml. ±SE
Pretreatment	6,100±1,240	276±38	21.3±4.1	6,795±1,640	302±73	20.3±3.7
1-5	333±94	89±16	47.9±3.7	228±95	72±11	43.7±6.2
6-10	27±5.0	51±9	53.3±5.3	18±6.2	50±22	60.0±3.2

TABLE 5.—*Outcome of Sixty-Eight Patients with Pneumococcic Meningitis Treated with Penicillin Alone or Penicillin Plus Streptomycin*

Diagnostic Group	Therapeutic Group: Penicillin Only — Total Patients	Penicillin Only — Deaths No.	Penicillin Only — Deaths %	Penicillin + Streptomycin — Total Patients	Penicillin + Streptomycin — Deaths No.	Penicillin + Streptomycin — Deaths %	Total — Patients	Total — Deaths	Total — %
Smear +	28	1	3.6	26	5	19.1	54	6	11.1
Smear neg., culture pos.	9	1	11.1	5	0	0	14	1	7.2
Total	37	2	5.4	31	5	16.1	68	7	10.3

Results

In Table 5 the constitution of the drug groups and the mortality rates have been tabulated. In spite of the fact that a higher percentage of the patients in the penicillin-streptomycin group died, the difference could occur by chance alone in at least one in five experiments. The greater number of penicillin-treated patients was caused by the facts that the first and last patient with a positive smear received the drug and that more of the empirically treated patients in the smear-negative group eventually proved to have D. pneumoniae in the cultures.

In spite of the fact that drugs with rapid action were chosen, because of the known tendency for deaths to occur within a few hours, the patients who died did so in a brief period, as shown in Table 4. Three of the seven patients died within 24 hours; two, within 48 hours, and one, within 72 hours. One of the patients who died within 12 hours of admission and the patient who died on the seventh day had ruptured brain abscesses. The latter patient was doing very well clinically, had regained consciousness, was free of neurologic findings, and was ambulatory. His spinal fluid had returned toward normal when the unsuspected abscess ruptured.

TABLE 6.—*Complications Among Sixty-One Patients with Pneumococcic Meningitis Who Recovered*

	Therapeutic Group			
	Penicillin Only (35 Patients)		Penicillin + Streptomycin (26 Patients)	
Complications	No.	%	No.	%
Neurologic deficit				
Mild	1	2.9	1	3.8
Mod.	0	—	1	3.8
Mental retardation with/without neurologic deficit				
Mild	1	2.9	1	3.8
Mod.	1	2.9	1	3.8
Subdural effusion	3	8.6	2	7.7
Total neurological	6	17.2	6	23.1
Miscellaneous				
Gastric hemorrhage	1	2.9	0	—
Penicillin reaction	1	2.9	0	—

In Table 6 are shown the complications which occurred. All of the neurologic complications mentioned represented the final evolution in patients who improved from a point of maximum dysfunction early in the course of illness. All of the subdural effusions occurred among the patients under 9 months of age and were managed by repeated needle aspirations until the fluid no longer accumulated.

In Table 2 it may be seen that there were insufficient differences in the mortality rates to indicate that there was an appreciable effect of age, even though there was a slight excess of deaths at the extremes of life. In Table 3 there is only a slight trend, which showed that the deaths occurred primarily among those patients who were very ill and sought hospitalization promptly or in those neglected five or more days.

Among the criteria of rapidity of response, the return of spinal fluid abnormalities toward normal and subsidence of fever may be used. In Tables 4 and 7 it can be seen that there was no appreciable difference in the two groups as far as these criteria were concerned.

In Table 8 the results obtained by the use of steroids before and after the alternate case study are given. Of the 7 deaths, 5 occurred among the 45 patients treated in the first period. Four of these patients were treated with steroids, three from admission until death. Only one patient who was judged to be ill enough to receive hormone treatment recovered when it was given. One

TABLE 7.—*Duration of Rectal Temperature Over 101 F After Start of Treatment*

	Treatment	
	Penicillin Alone	Penicillin + Streptomycin
Patients with temperature below 101 F, %		
Within 72 hr.	33%	45%
From 73-144 hr.	56%	36%
After 144 hr.	11%	19%
Temperature below 101 F, hr.		
Range	12 - 240	24 - 576
Mean±SE	107±11.8	135±43.5

TABLE 8.—*Use of 11-OH Corticosteroids in Pneumococcic Meningitis*

Reason for Steroid Use	Antibiotic Group	Steroid Treated			No Steroids Used		
		Pts., No.	Died, No.	Died, %	Pts., No.	Died, No.	Died, %
Routine as part of alternate case study	Penicillin alone	6	0	0	6	0	0
	Penicillin + streptomycin	5	1	20	6	1	16.7
Patients selected because of critical illness	Penicillin alone	2	2*	100	23	0	0
	Penicillin + streptomycin	3	2	67	17	1	5.9

* Steroid treatment delayed in 1 patient until 36 hr. after admission.

other patient in whom the drug was not used died. As can be seen, these results were not influenced by the antibiotics used.

On the other hand, among 23 patients in the alternate case study there was no difference in the mortality rate between those patients who were treated with hydrocortisone and those who were not. Moreover, of the three patients with neurological complications, two were in the steroid group and one in the control group.

Comment

Among the acute bacterial infections, pneumococcic meningitis still has one of the highest rates both for deaths and for serious complications. It is our impression from experience in a large city hospital, compared with this experience in a specialized contagious disease hospital, that much of the difficulty stems from the nature of the patient who is admitted with this disease. The markedly different results in several clinics also suggest this conclusion. The patients reported in this study who died, except for the patient who had a delayed rupture of a cerebral abscess, were essentially moribund on admission. None of these patients evidenced any real improvement, and, in most, life was simply prolonged by pressor substances, restoration of electrolyte balance, tracheostomy, and even artificial respiration in hope that the antibiotics would have time to be effective. It is noteworthy that among these patients, where the death rate was low, the tendency for deaths to occur at either end of the life span is not as clear as among our previous patients with a higher death rate.[4,11] However, delay in diagnosis and hospitalization for five days or more seemed an important factor in about half of the deaths. Several other deaths occurred among patients who became rapidly and violently ill and were therefore treated early in the chronological sense but late in the pathologic sense.

In spite of the impression that host factors are paramount, it still seems important to continue to try to improve the treatment regimen. The over-all mortality rate in this series indicated that penicillin, in the dose used, was very satisfactory. However, the number of patients who died plus the number who had neurologic complications constituted about a third of those treated. Thus, there is still considerable hope for salvage if progressive infection is a significant factor. We have previously reported that the combination of intravenous chlortetracycline with penicillin was probable harmful [11] and have been disappointed in the effectiveness of added sulfonamide and/or the intrathecal use of penicillin, even though the documentation of the failure of the latter two was not as well controlled as the former.

In the present study, the results indicated that streptomycin as used did not increase the effectiveness of penicillin. Even though the number of patients was not large, the combined incidence of deaths and neurologic damage should have allowed the demonstration of a significant effect had there been one. A small increment of benefit could have been missed, but, with the figures obtained and the fact that the initial trend was unfavorable in the combination group, too

large a group of patients would be needed to demonstrate an effect to make the continuation of the study practical. It seems likely from these results that once the level of antibiotic activity achieved by the penicillin regimen used in this study is reached further antibiotic action is of little benefit. Rapidity of antibacterial effect may be more important than height of the level, after a certain threshold has been obtained. Therefore, this study used a pair of drugs which should have been most rapidly bactericidal. Our evidence has indicated that streptomycin in the doses used does penetrate the inflamed meninges, as does penicillin. In addition, prior experience has shown that high-dose parenteral therapy with penicillin gave better results than low-dose parenteral therapy plus sulfonamides and intrathecal penicillin.[4] Moreover, there are inherent risks with intrathecal therapy, which we have repeatedly encountered when a large number of patients were treated. On the other hand, the problem of whether intrathecal penicillin and streptomycin in addition to the parenteral drugs, as used, would have been useful cannot be answered with complete assurance. There are many other combinations of drugs, administered systematically and/or locally, which could be explored, but from the studies to date there is no reason for great hope of success. Patient 6, in Table 1, is an example of the failure of multiple antibiotics.

Since it is likely that much of the damage that occurs in these patients is related to the intensity of the inflammation which continues even after the drugs have begun to remove the bacteria, it has seemed logical to try to minimize such damage by the use of adrenal steroids. As can be seen in Table 8, when these were used empirically in the patients who were felt to be near death their use was of little help. Thus, in all patients who died, except one, it was possible to start the hormones either on admission to the hospital (in three patients) or at least 12 hours prior to death (in one patient). The criteria for starting the use of the drugs were strict enough that only one patient who was felt to be eligible for treatment survived. Because of this minimal evidence of benefit it seemed important to ascertain if there was any way in which these drugs could be used which would establish their worth or perhaps document their ineffectiveness and potential hazard. Since a major deterrent to the effectiveness of hydrocortisone may have been delay in its use, it was logical to study the results when the drug was started on admission to the hospital. In order to evaluate this regimen, however, when there is a high recovery rate without steroids, a control group was necessary. From the data presented it is apparent that we have not been successful in documenting that the steroid hormones have a beneficial effect in this disease when used routinely and promptly on admission. On the other hand, in these patients, who were not as critically ill as those we have previously reported,[22] the complications, such as secondary infections, have not been as great. However, since the complications of steroid therapy must be evaluated as well as the therapeutic results and since bias may easily influence the avidity for which evidence of complicating infections, such as those of the urinary tract, are sought, studies like this may be done better by a double-blind technique. This procedure is now being used.

Summary

In the period covered by this report 74 patients with pneumococcic meningitis were admitted to the hospital. Six of the patients were not used in the experimental alternate case study because of inability to start therapy in time, misdiagnosis, or prior extensive treatment. Among 68 other patients, 37 were treated with penicillin and 31 with penicillin and streptomycin. There were two deaths in the penicillin group and five in the combination group.

There were six patients with neurologic complications in each group. Of these, three were permanent in the penicillin group and four, in the streptomycin-penicillin group.

There were no differences between groups in the rate of return of the spinal fluid toward normal and in the subsidence of fever.

The death rate was somewhat higher among the patients under 6 months and over 50 years of age, but the trend was not significant. Similarly, those patients who had been ill only one or two days or more than four days had somewhat higher death rates.

Among the first 45 patients, only one patient died who did not receive steroids. One patient received the hormone 36 hours after admission, 12 hours before death. Another four patients were treated with this hormone on admission because of a grave condition. Only one of these recovered.

The last 23 patients were treated alternately with hydrocortisone. Only one patient in each group died. There were no differences found among the other estimates of response.

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Rectal Cortisol in the Therapy of Ulcerative Colitis

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The successful use of topical steroid therapy in diseases of the eye, skin, and joints has led to an evaluation of the effect of cortisol enemas in idiopathic ulcerative colitis. Observations from this laboratory have implied negligible absorption of cortisone from the rectum in ulcerative colitis, and so a relative absence of side-effects was to be anticipated.[1] Truelove and others have reported encouraging results with rectal hydrocortisone in ulcerative colitis.[2,3] This report represents an attempt to define the type of patient in whom such therapy might be most helpful.

Methods

All 16 patients studied had the diagnosis of ulcerative colitis confirmed by sigmoidoscopy and x-ray examination at either the Grace-New Haven Community Hospital or the West Haven Veterans Administration Hospital. Stool examinations were performed to exclude amebiasis, bacillary dysentery, and other causes of diarrhea; many patients had received antiamebic therapy on an empirical basis. Table 1 illustrates an arbitrary classification of ulcerative colitis that we have used in assessing our results.

Seven of the patients received a daily enema of 100 cc. of isotonic saline during a control period of 7-10 days. Because of time and financial limitations, nine patients were started directly on cortisol retention enemas. Steroid enemas were prepared by dissolving 200 mg. of hydrocortisone hemisuccinate* in 100 cc. of isotonic saline and were given by slow rectal drip from an infusion bottle at the bedside. Such treatment was, in general, carried out for a two-week period and then stopped. During the period in which rectal hydrocortisone was given, therapy was otherwise unchanged.

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* Supplied as Solu-Cortef by Dr. H. Peltier, of Upjohn.

TABLE 1.—*Classification of Severity of Patients with Ulcerative Colitis*

1. No symptomatology; granular mucosa; previous history of disease
2. Mild cramps; up to 3-4 nonbloody bowel movements per day; sigmoidoscopy granular; normal physical activity
3. Moderate to severe cramps; more than 4 bowel movements per day; occasional blood and mucus noted in stool; less than normal physical activity
4. Moderate to severe cramps; more than 8 bowel movements per day; bloody mucoid discharge; sigmoidoscopy, friable ulcerated mucosa; moderately to markedly incapacitated
5. Marked to severe incapacity with more than 12-15 bowel movements per day; severe anemia; frequent hospitalizations required
6. Acute fulminating, requiring surgical therapy

Patients did not know when hydrocortisone was substituted for saline enemas. The effect of the enemas was evaluated by sigmoidoscopy prior to therapy, after the control period, and at 7 to 14 days after the administration of hydrocortisone. Psychologic well-being, appetite, the character of the stools, and the amount of bleeding were also evaluated. In five patients, cortisol levels were measured in the blood; these results have been reported in detail previously.[1]

Results

No obvious improvement was noted in the patients during the course of saline enemas; sigmoidoscopic appearance was unchanged despite bed rest, enthusiasm, and hospital care. In 8 of the 16 patients treated with cortisol enemas, a satisfactory result was obtained. In such cases, bowel movements quickly diminished to one or two daily, blood and mucus disappeared promptly, and the friable ulcerative mucosa was replaced by a mildly granular surface with no evidence of blood or mucus. If the patient was to show a satisfactory response, prompt subsidence of acute symptoms usually occurred within a matter of 24 to 48 hours after initiation of cortisol enemas. Of some interest was the general absence of euphoria and sense of

TABLE 2.

Patient	Extent of Involvement	Duration of Illness	Gradation	Response
1	Rectum, rectosigmoid	9 mo.	4	(*a*) Excellent, immediate, relapse after 5 days (*b*) 2d course-excellent response, again with relapse after 2 wk. of therapy
2	Entire colon	5 yr.	4	Fair response, moderate decrease in diarrhea, bleeding, etc.; better than when compared with response to intravenous corticotropin
3	Descending colon, rectum, rectosigmoid	11 mo.	3	(*a*) Excellent response, relapse after 2 days without therapy (*b*) Excellent, relapse (*c*) Failure, required 8 to 10 days of intravenous corticotropin for slight improvement
4	Entire colon	2 yr.	4-5	Failure, surgery (total colectomy & ileostomy)
5	Rectum, rectosigmoid	1 yr.	3	Failure, moderate response to intravenous & parenteral steroids
6	Entire colon	10 yr.	6	Failure — surgery; total colectomy
7	Rectum, rectosigmoid	5 yr.	3	Excellent
8	Rectum, rectosigmoid	3 yr.	2	Excellent
9	Rectum	6 mo.	2	Excellent
10	Transverse colon, descending colon, rectosigmoid, rectum	3 mo.	2	Excellent
11	D, rectosigmoid, rectum	2 yr.	2-3	Excellent
12	Rectum, rectosigmoid	3 yr.	2-3	Excellent
13	Descending colon, rectosigmoid, rectum	2½ yr.	3	Moderate improvement initially but not complete
14	Entire colon	5 wk.	5	Very good
15	Entire colon	6 yr.	2-3	Excellent but transient
16	Entire colon	4 yr.	2-3	Fair; stopped after 4 days & started on intravenous corticotropin with excellent response

well-being or of markedly improved appetite, symptoms frequently associated with the parenteral use of steroids.

Five patients showed less moderate improvement following cortisol enemas. There was reduction in the number of daily movements from 8-12 per day down to 4 or 5, but blood or mucus persisted in the stool. Two of these patients had at first a very dramatic response to therapy but relapsed when therapy was discontinued.

Four patients failed to show any response. Two of these patients continued to be refractory to intravenous corticotropin (ACTH) and underwent total colectomy and ileostomy. One patient with mild to moderate severity failed to show a satisfactory response to rectal hydrocortisone and also a less than optimal response to intravenous and oral steroid therapy and has continued with a nonremitting low-grade clinical course.

Follow-up study in the patients who did well, now of 6-15 months' duration, has not yet demonstrated an exacerbation of colitis (but this should not be ascribed to the effect of rectal hydrocortisone). One patient who had an excellent response to the first trial of therapy failed to respond as well to a second course and failed to respond at all to a third course of therapy. Changes in her environment and the administration of oral steroids have subsequently resulted in a complete remission in this case.

Comment

In general, patients with disease of mild to moderate severity limited to the rectum or rectosigmoid, displayed a satisfactory clinical response to rectal hydrocortisone; within 48 to 72 hours, the number of bowel movements decreased and gross bleeding and cramps also disappeared. Prompt disappearance of fever, euphoria, and greatly improved appetite, frequently noted with intravenous corticotropin, were not particularly seen in this series. As the patient improved, fever gradually subsided.

Sigmoidoscopy, carried out from three to seven days after therapy was started, disclosed marked improvement; friability and

bleeding mucosa became granular and nonfriable, similar in appearance to that of patients with ulcerative colitis in remission. This appearance seemed to come on more quickly than with intravenous steroids.

Patients with disease of long-standing, marked severity or extensive involvement usually failed to show a satisfactory response to rectal hydrocortisone, and in such cases intravenous corticotropin seems preferable.

The relative lack of absorption after rectal instillation of cortisol would imply that any beneficial effect of rectal hydrocortisone is primarily a local one. Previous studies, in which serial plasma levels of free cortisol and its conjugated derivatives were determined, revealed a relative plateau of free cortisol. That small changes in blood-steroid level have a pharmacological effect has not been demonstrated. Since biological activity has been attributed only to the unconjugated steroid, it was concluded that this mode of administration was relatively devoid of the physiologic systemic effects of parenterally or orally administered steroids. Rectal hydrocortisone, therefore, may be of value in patients with relative contraindications to the use of steroid therapy. Thus, in Patient 12, who had failed to respond to conservative management, the past history of tuberculosis and peptic ulcer made the use of intravenous steroids unwise. Ten-day administration of saline enemas produced no improvement in his clinical picture, but there was a prompt and dramatic response to rectal hydrocortisone. This response has persisted over a period of 10 months. Case 6 had developed marked psychotic behavior on intravenous and oral steroid therapy but showed no evidence of psychosis during the three days of rectal hydrocortisone. She had, however, no clinical response to rectal hydrocortisone. Psychosis recurred immediately after intravenous corticotropin, and the patient underwent total colectomy. Patient 9, with severe rheumatoid arthritis, failed to show any amelioration of her arthritic complaints during the administration of rectal hydrocortisone, an observation which again implies a nonsystemic effect.

Two patients in our series responded to steroid enemas but relapsed within 48 hours after cessation of therapy. Thus, Patient 1 was unable to be maintained on 20 mg. of prednisone orally after an initial four to five days of steroid enemas. She was subsequently controlled with intravenous corticotropin and oral hydrocortisone, but on this regimen reexacerbation occurred, which failed to respond to increase in oral dosage of steroid. Hydrocortisone enemas were again instituted; after three days of therapy stools became formed, with associated subsidence of cramps and bleeding. Sigmoidoscopy disclosed only a granular, nonfriable mucosa in contrast to the originally very friable ulcerated mucosa covered with blood and mucopurulent exudate. The patient again relapsed while in the hospital two to three days after rectal therapy was discontinued and has been only fairly well controlled with oral steroids.

What are the criticisms of this mode of therapy? Certainly ulcerative colitis has an unpredictable course; spontaneous remission does occur, and it has been suggested that in 50% of patients any form of therapy will bring about improvement.[3] Obviously, anything one does for a patient with ulcerative colitis may make him better and a degree of specificity should not be too aggressively claimed for this form of therapy. However, the prompt remission following the institution of hydrocortisone enemas, together with a failure of patients to respond to saline controls, does suggest that a specific topical anti-inflammatory effect plays a role. Certainly symptoms in ulcerative colitis may quickly respond to nonspecific therapy; yet we have been impressed by the rapid improvement of the sigmoidoscopic picture, more rapid than we have associated with other forms of therapy. Bringing the medicine to the disease in so obvious a fashion as rectal hydrocortisone may lead to remarkable psychogenic effects, and the supposed benefits of other forms of topical therapy in ulcerative colitis in the past must be remembered. The harm done to patients by concentrating so specifically on the rectum must

also be considered, and specifically we would not advise such therapy in children without clear consideration of the psychic factors involved.

What are the indications for rectal hydrocortisone? The ideal patient would seem to be one who has disease limited to the rectosigmoid of relatively brief duration, certainly less than two years. Hydrocortisone enemas under these circumstances appear to be as effective as any other form of treatment presently available and offer the advantages of rapidity of response and the absence of complicating side-effects. It may well be, however, that rectal hydrocortisone should be tried in all but the most debilitated patients, with proven ulcerative colitis, for a minimal period of 72 hours and if possible for 5 to 7 days. Failure to respond in this length of time dictates the use of intravenous steroids and may be of prognostic importance; speculation that such patients will eventually require surgery may be in order.

Intravenous steroids are preferable in patients with very long-standing disease or extensive involvement of the colon. Parenteral steroids are also preferable in the debilitated patient where the side-effects of increase in appetite and euphoria have clinical advantages. The duration of therapy and the wisdom of instituting periodic treatment with rectal hydrocortisone even when symptoms are absent are factors which cannot be evaluated at the present time.

Summary

Observation of the effect of rectal hydrocortisone in 16 patients with chronic ulcerative colitis revealed a satisfactory response in 8 patients. When administered in a dose of 200 mg. of hydrocortisone daily the enemas brought about a prompt response within 48 to 72 hours. A satisfactory response may be expected in those patients with disease of limited involvement and short duration. In view, however, of the relative safety of this form of therapy, it is suggested that it should be considered as the initial steroid therapy in many patients with chronic ulcerative colitis.

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Case Reports

Clinical and Laboratory Correlation in Severe Autoimmune Hemolytic Anemia

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With the Technical Assistance of Estelle M. Downer, M.S., and Jean E. Hinz, A.B.

During the past 50 years, an abundant literature has been directed to various aspects of autoimmune hemolytic disease. Recognition and measurement of changes in erythrocyte life span,[1] improved methods for demonstration of erythrocyte autoantibody,[2] and advances in knowledge of bile pigment metabolism[3] have facilitated diagnosis and understanding of this disorder. Fortunately, most clinical and hematologic manifestations of autoimmune hemolytic disease are correctible by treatment with the corticosteroids,[4,5] even though evidences of autosensitization of erythrocytes may persist. On the other hand, the existence of inordinately severe cases which prove resistant to therapy have provided further opportunity to observe the natural course of the disease. We have studied a patient in whom continuous production of autoantibody in high titer resulted in constant anemia, reticulocytosis, and icterus, despite intensive treatment with corticosteroids. These exaggeratedly abnormal laboratory values lent themselves particularly well to a study of the effects of "autosensitization" of erythrocytes on their rate of destruction and on the subsequent development of the hemolytic syndrome.

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In this study, the question was considered of whether severity of hemolytic anemia could be correlated with the amount and type of autoantibody demonstrable. The rate of sensitization of normal erythrocytes when injected into the patient was determined in order to provide information relative to the in vivo specificity of autoantibodies. The role of the spleen as producer of antibody was compared to that of the other fixed tissues in the pathogenesis of immune hemolytic anemia. The object of this report is to present the results of these studies.

Report of Case

Clinical Data.—A 38-year-old Negro meat packer became ill rather suddenly in November, 1953, with dyspnea, cough productive of a yellowish sputum, and fever. The patient was treated with antibiotics for pneumonia by his family physician and for a while appeared to improve symptomatically. However, one month later he was told that his eyes looked "yellow." Progressive weakness obliged him to give up his job to do less exhausting work. In January, 1954, the patient became bedridden because of profound weakness, which soon progressed to air hunger.

On physical examination, this man was extremely ill, hyperventilating, and dyspneic. There was marked pallor of the mucous membranes, and the sclerae were icteric. Dullness and medium moist rales were found in the left upper lobe. The heart was rapid and regular. A loud systolic murmur was present at the base. The liver and spleen were palpable 6 and 10 cm. below their respective costal margins.

Initial Laboratory Studies.—Hematologic studies on admission showed a hemoglobin value of 2.6 gm. per 100 cc. The red blood cells numbered 720,000 per cubic millimeter. The leukocytes were 23,000 per cubic millimeter, with segmented neutrophils 38%, band forms 51%, lymphocytes 3%, and monocytes 8%. There were 58 normoblasts per 100 leukocytes The blood smear showed consider-

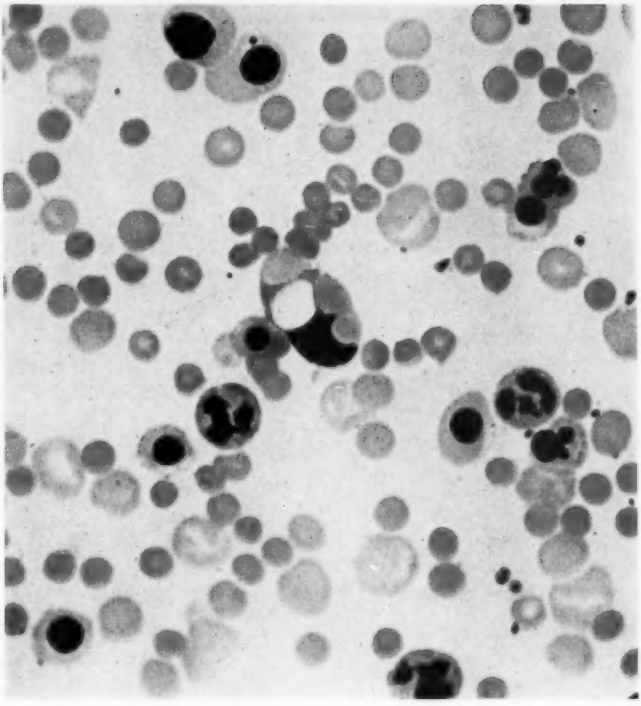

Fig. 1. — Peripheral blood smear, showing spherocytosis and erythrophagocytosis; reduced about 10% from mag. × 500.

able spherocytosis, polychromatophilia, and evidences of erythrophagocytosis (Fig. 1). Platelets numbered 43,000 per cubic millimeter, and the reticulocyte count was 29%. The bone marrow aspirate showed enormous hyperplasia of normoblasts. Granulocytes and megakaryocytes showed less increase in number. A bone marrow and three peripheral blood preparations were all negative for lupus erythematosus (L. E.) cells. The total serum bilirubin was 12.4 mg. per 100 cc., of which 4.5 mg. constituted a one-minute-reacting fraction. A 24-hour collection of urine showed 307 mg. of urobilinogen, and a four-day collection of stool showed an average excretion of 2,334 mg. per 24 hours. The urine showed no hemoglobin and hemosiderin. Osmotic fragility of freshly drawn blood showed beginning hemolysis at 0.48 and complete hemolysis at 0.32% sodium chloride. Mechanical fragility of fresh blood was under 1%. After 24-hour incubation at 3 C, osmotic fragility was unchanged and mechanical fragility was 7.6%. Incubation at 37 C resulted in hemolysis so that osmotic or mechanical fragility studies could not be made.

Paper electrophoresis showed type A hemoglobin. Alkali-resistant hemoglobin was 0.6%. A sickle-cell preparation was negative.

The Mantoux test was negative. Examination of the sputum by smear and culture showed no pathogenic organisms. Four blood cultures showed no growth. Agglutination studies for Brucella, typhoid, and paratyphoid organisms were all negative. Antibodies to the virus of lymphocytic choriomeningitis, psittacosis, Q-fever, and influenza A and B were not demonstrated. However, there was a positive complement-fixation test against the virus antigen of mumps in a titer of 1:256.

The cephalin-cholesterol flocculation test was 4+. The thymol turbidity test was 9.0 units. Serum cholesterol was 70.2 mg. per 100 ml., of which 28.5% was esterified. The total protein was 7 gm. per 100 cc., with albumin 3.3 gm. and globulin 3.7 gm.

Muscle and lymph node biopsy showed no pathologic changes. A chest plate confirmed the presence of pneumonia in the left upper lobe. The patient was Type A, Rh-positive.

Attempts to cross match this patient's blood for transfusion met with failure, as the serum agglutinated all types of erythrocytes at all temperatures (Table 1). In Table 2 is depicted the effect of fresh Type AB Rh-negative serum on the patient's untreated and trypsinized erythrocytes. Hemolysis of trypsinized normal red cells occurred in the patient's fresh serum diluted to 1:32 in Type AB serum. The patient's washed erythrocytes hemolyzed promptly when brought into contact

TABLE 1.—*Serum Agglutination of Autogenous and Control Erythrocytes Under Various Experimental Conditions at Time of First Hospital Admission*

Serum Dilution	Agglutinins															
	Auto-Sal.			Auto-Alb.			Auto-Tryp.			Iso-Sal.			Iso-Alb.		Iso-Tryp.	
	3 C	20 C	37 C	3 C	20 C	37 C	3 C	20 C	37 C	3 C	20 C	37 C	3 C	20 C	37 C	3 C	20 C	37 C
1:1	3+	2+	±	3+	2+	1+	4+	3+	2+	4+	2+	±	3+	3+	1+	4+	3+	2+
2	3+	2+	±	3+	2+	1+	4+	3+	2+	4+	1+	±	4+	3+	1+	4+	3+	2+
4	3+	1+	±	3+	2+	2+	4+	3+	2+	4+	0	0	3+	2+	1+	4+	3+	2+
8	3+	1+	0	3+	2+	2+	4+	3+	2+	3+	0	0	3+	1+	1+	4+	2+	2+
16	3+	1+	0	2+	2+	1+	4+	3+	2+	2+	0	0	3+	1+	1+	4+	2+	1+
32	2+	±	0	2+	1+	1+	3+	2+	2+	1+	0	0	2+	±	±	3+	1+	1+
64	2+	±	0	1+	1+	1+	2+	2+	1+	1+	0	0	1+	0	±	2+	1+	1+
128	2+	0	0	1+	±	±	2+	1+	1+	1+	0	0	±	0	0	2+	0	1+
256	1+	0	0	±	±	0	1+	1+	1+	±	0	0	0	0	0	1+	0	±
512	±	0	0	±	±	0	1+	±	1+	0	0	0	0	0	0	1+	0	0
1,024	0	0	0	0	±	0	±	0	±	0	0	0	0	0	0	±	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

TABLE 2.—*Titration of Patient's Serum at First Hospital Admission, with Use of Fresh Type AB Rh-Negative Serum as Diluent for Hemolytic Activity*

Serum Dilution	Autoagglutinin		Isoagglutinin	
	Untreated	Trypsin	Untreated	Trypsin
1:1	3+H	4+H	0	3+
2	3+	4+	0	3+
4	3+	3+	0	3+
8	2+	3+	0	2+
16	2+	3+	0	2+
32	1+	3+	0	1+
64	±	2+	0	±
128	0	2+	0	0
Con.	0	2+	0	0

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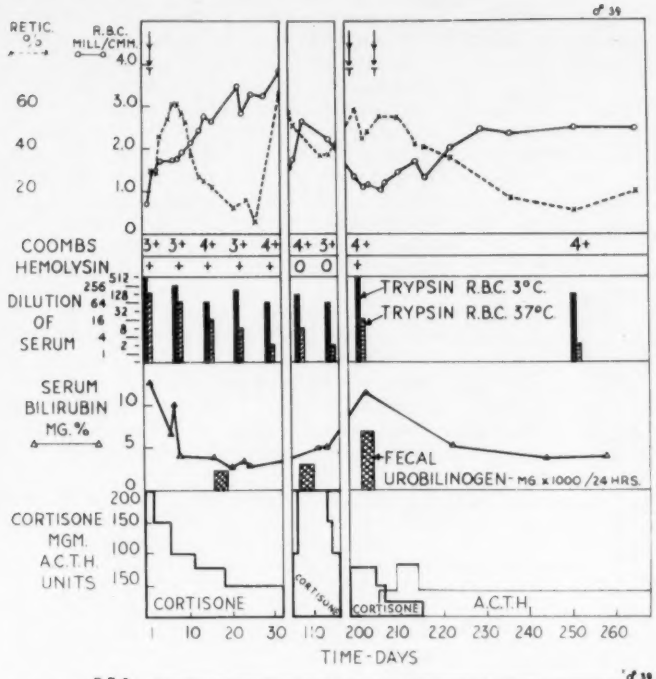
with fresh complement. Heat inactivation of diluting serum prevented hemolysis, which demonstrated hemolytic activity both in the patient's serum and also attached directly to the erythrocytes. The strongly positive (4+) antiglobulin test was inhibited by human γ-globulin (1:4,096),[9] indicating that the protein attached to the erythrocytes was γ-globulin in origin.

Course (Fig. 2).—Therapy was initiated with cortisone, 200 mg. daily, diminished stepwise every third day, until a daily maintenance dose of 50 mg. was given. Almost immediately, the reticulocytes began to increase and reached a peak of 60.4% on the 5th day of treatment and then declined to a low point of 4% on the 23d day. The red cell count and hemoglobin increased steadily to 3,850,000 and 11 gm. per 100 ml. on the 35th day of observation without the use of blood transfusions other than 2 units given at the beginning of hospitalization. The serum bilirubin fell to 2.8 mg. per 100 cc. The Coombs antiglobulin test remained markedly positive (4+). Autohemagglutinins not demonstrated with saline dilution at 37 C were active against trypsinized test erythrocytes in a dilution of 1:2.

The patient remained in excellent control through March, 1954. On April 29, he entered the clinic weak, fatigued, pale, and icteric and admitted to having discontinued therapy with cortisone abruptly the previous month. Evidence of increased hemolysis was present; the hemoglobin was 7.5 gm. per 100 cc.; the erythrocytes, 1,750,000 per cubic millimeter; the reticulocytes, 12.6%, and the spleen, 10 cm. below the costal margin. The fecal urobilinogen output had risen to 3,000 mg. daily. The dosage of cortisone was increased to 200 mg. daily and gradually was diminished to 75 mg. daily. The patient failed to make a substantial improvement. He was admitted to the hospital in August, 1954, with fever, chills, weakness, dull pain in the



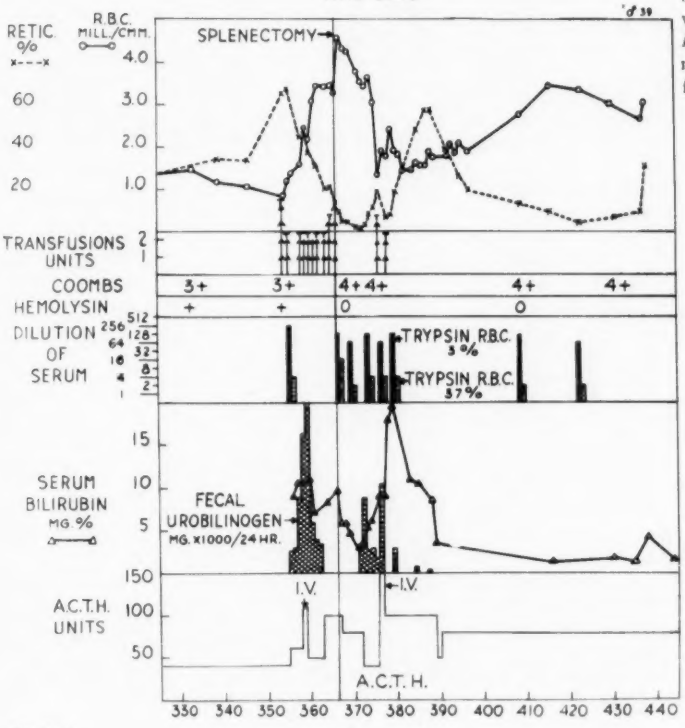


Fig. 2.—*A*, early response of laboratory values to corticosteroids. *B*, laboratory values immediately preceding and following splenectomy.

splenic area, and malaise. On this admission, the erythrocytes numbered 1,330,000 per cubic millimeter; hemoglobin, 4.75 gm. per 100 ml.; reticulocytes, 58%, and total serum bilirubin, 11.4 mg. per 100 ml. Group O normal erythrocytes were agglutinated in saline in titers of 1:32 (3 C) and 1:2 (37 C). Trypsinized Group O erythrocytes were agglutinated in titers of 1:512 (3 C) and 1:16 (37 C). A strong (4+) hemolysin remained in undiluted serum and the antiglobulin test was 4+.

Cortisone, no longer effective, was gradually diminished and replaced by corticotropin (ACTH), 80 units daily, intramuscularly. For the next three months, the patient appeared to compensate for hemolysis, and in November, 1954, the red cell count reached 3,050,000 per cubic millimeter. The hemolysin could not be demonstrated, and the titer of hemagglutinins against trypsinized erythrocytes fell to 1:2 (37 C). However, in December, 1954, while the patient was still on corticotropin, the hemoglobin value fell to 4.5 gm. and the erythrocytes to 1,380,000 per 100 ml. Concomitantly, the patient was very weak and icteric and the spleen enlarged further to 14 cm. below the costal margin. It was apparent that the illness could not be controlled with corticotropin. It was elected to perform splenectomy in the hope that the illness might be controlled with smaller doses of corticosteroids.

The patient was prepared for surgery with 2 units of blood, daily, and with corticotropin, 100 units intravenously, in addition to the repository corticotropin injection (corticotropin gel), 80 units intramuscularly, daily. When the erythrocyte count reached 4,000,000 per cubic millimeter, splenectomy was performed (Fig. *2B*).

The surgically removed spleen weighed 800 gm. The sinusoids were stuffed with erythrocytes, and myeloid metaplasia was very pronounced. There was swelling of the vascular endothelium. There was no specfic histologic evidence for any acute infections or chronic granulomata. Culture of the spleen for pathogenic organisms, fungi, protozoae, spirochetes, and viruses was not productive.

During the first week after splenectomy the erythrocyte count dropped slightly, with no change in the titer of autoantibodies. On the other hand, the hemolysin could not be demonstrated. One week postoperatively, the erythrocyte count suddenly dropped to 1,320,000. The reticulocytes rose to 58%. At this point, large numbers of normoblasts were released into the circulation and reached a peak of 680 per 100 leukocytes. The patient became increasingly icteric, and the fecal urobilinogen output rose to 10,000 mg. in 24 hours. During this crisis, there was no increase in titer of autoantibodies.

The patient was given corticotropin, 100 units intravenously, in addition to 100 units of repository corticotropin injection, which he had been taking intramuscularly. In 10 days, the circulating normoblasts diminished to 12 per 100 WBC; the reticulocytes fell to 4%, and the red cell value remained between 1,700,000 and 2,000,000 per cubic millimeter. On March 28, the patient experienced a severe pain in the left shoulder and his temperature increased to 106 F. There was dullness at the base of the left lung posteriorly. He received erythromycin, 800 mg. daily, and seemed to improve. He remained in a state of relative well-being throughout April, 1955. The hemoglobin remained 9 gm. per 100 ml. and the red cell count 3,340,000 per cubic millimeter. There was no change in the titer of auto- and isoantibodies. The antiglobulin test remained 4+, and hemolysin could not be demonstrated. Mechanical fragility was 14.9%. Heretofore, platelet agglutinins could not be found, but the patient's serum now agglutinated platelets from compatible blood in a dilution of 1:4.

On May 12, 1955, he was admitted for the last time with severe frontal headache and a spiking fever was present. Erythromycin was again given, 800 mg. daily, but seven days after admission, the patient had a convulsion and died.

Autopsy findings showed a subdiaphragmatic abscess under the left leaf of the diaphragm, left frontal sinusitis, and leptomeningitis. Other autopsy findings were all consistent with severe hemolytic anemia but cast no light on any underlying disease process which might account for "autoimmunization."

Experimental Observations

Erythrocyte Survival Studies.—On the first hospital admission, the life span of transfused erythrocytes was determined to be 11 days by the Ashby technique.

Prior to surgery, the patient was transfused daily with Group O erythrocytes so that their survival time could be followed by differential agglutination. Inagglutinable-cell counts were performed twice a day. About half of the transfused cells disappeared in a 12-hour period (Fig. 3). On two occasions, all of the transfused cells disappeared in 12 hours. During this period of time, there was an increase of the serum bilirubin to 11 mg. per 100 ml. Daily examination of the stools for urobilinogen showed a steady increase, which reached a peak excretion of 20,000 mg. in 24 hours (Fig. 2), which probably represented hemolysis of the transfused erythrocytes.

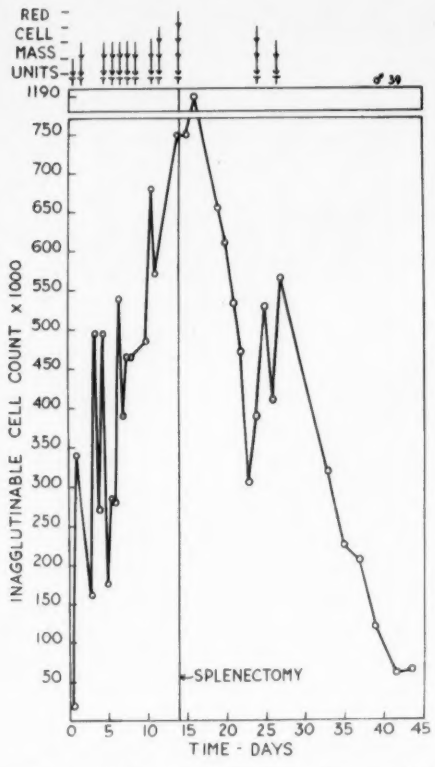


Fig. 3.—Effect of splenectomy upon survival time of transfused erythrocytes.

Surgery had no effect on the life span of the transfused cells. Although the slope of the erythrocyte-disappearance curve became less steep, all transfused erythrocytes were completely gone in 13 days (Fig. 3).

In Vivo Rate of Sensitization of Normal Erythrocytes.—The patient's freshly centrifuged erythrocytes were washed four times with warm 0.85% sodium chloride solution and recentrifuged at 3,500 rpm for 30 minutes; all possible saline was removed. The packed erythrocytes were resuspended in 0.85% saline to give a hematocrit reading of exactly 40%, and inagglutinable-cell counts were performed with antiglobulin serum and anti-A serum. Base-line inagglutinable-cell counts, repeated daily for five days were found to be constantly 100,000 with antiglobulin serum and 45,000 per cubic millimeter with anti-A serum. Two units of Group O Rh-negative normal erythrocytes were then given. Inagglutinable-cell counts as above were taken immediately after the transfusion and repeated daily. After the second pint of blood, the inagglutinable-cell count determined with antiglobulin and anti-A sera rose to 615,000 and 700,000 per cubic millimeter, respectively (Fig. 4). On the second day, the antiglobulin serum inagglutinable-cell count fell sharply, while the anti-A-cell count diminished 24 hours later. This indicated that transfused normal red cells became coated with globulin within 24 hours and that sensitization in vivo preceded destruction by about one day. Following these initial drops in the inagglutinable-cell counts, a leveling of these values was observed until the seventh day, when all traces of transfused blood disappeared from the circulation.

Serologic Studies.—Data relative to the characteristics of the auto-antibodies will be found in Tables 1, 2, and 3. Before treat-

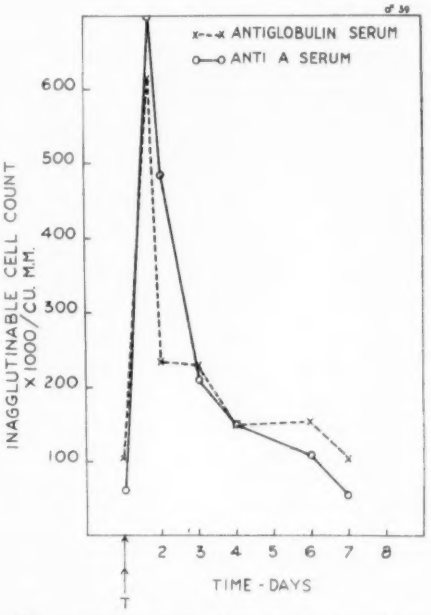


Fig. 4.—In vivo comparison of rate of sensitization of normal erythrocytes and disappearance of transfused cells. Ashby technique with use of antiglobulin serum and anti-A serum.

TABLE 3.—*Titers of Agglutination of Normal Red Cells by Patient's Serum Under Various Conditions over Course of Illness*

Date	Saline			Albumin			Trypsin			Hemolysin
	3 C	20 C	37 C	3 C	20 C	37 C	3 C	20 C	37 C	
1/21/54	128	2	2	64	16	16	512	64	128	+
1/27/54	16	0	0	16	0	1	256	128	64	
2/3/54	4	—	0	16	1	1	64	16	16	
2/11/54	4	0	0	4	1	0	128	8	8	+
2/16/54	8	0	0	8	1	0	64	8	2	+
2/25/54	16	—	0	16	—	4	128	—	4	
5/6/54	16	0	0	32	4	4	128	16	8	±
5/13/54	8	0	0	8	4	1	64	4	2	+
6/3/54	8	0	0	32	4	8	128	16	8	+
8/17/54	32	1	2	128	16	8	512	16	16	+
10/7/54	4	0	0	16	1	1	128	4	2	—
11/4/54	8	—	0	16	—	2	64	—	2	0
12/2/54	4	—	—	8	—	—	16	—	—	+
12/16/54	32	4	8	16	8	16	64	16	32	+
12/30/54	4	—	—	8	—	—	64	—	—	—
2/18/55	64	—	1	64	—	4	256	—	4	+
3/2/55	32	1	2	—	—	—	128	16	8	—
3/4/55	8	0	0	8	4	1	64	8	2	—
3/10/55	16	0	0	—	—	—	64	4	4	—
3/12/55	8	1	0	16	2	2	128	8	4	±
4/14/55	32	0	0	32	4	2	128	4	2	0
4/28/55	8	—	0	16	—	4	64	—	2	

ment was started, the patient's serum agglutinated his own erythrocytes, as well as a test panel of erythrocytes of all serologic types (Table 1). Treatment with corticosteroids resulted in a virtual disappearance of saline-reacting warm agglutinins, but agglutinins against trypsinized erythrocytes persisted for the entire illness (Fig. 2).

Trypsinization of test erythrocytes enhanced the hemolytic activity of the patient's serum in the presence of complement.

The Coombs antiglobulin test was at all times strongly positive (4+) and was inhibited by 4% human γ-globulin in a dilution of 1:4,096 which affirmed that the substance which coated the erythrocytes was derived from the γ-globulin fraction of serum.

During the postoperative period, the release of a large number of normoblasts afforded an opportunity to isolate these cells from the peripheral blood stream by differential centrifugation and to study their immunologic reactions in vitro. This experiment was reported in detail elsewhere.[7] The normoblasts were agglutinated by anti-A and by anti-M serum, which corresponded to this patient's blood type. Agglutination also occurred when the normoblasts were treated with antiglobulin serum, with the patient's serum, and with a serum which contained a cold agglutinin. The titer of normoblast agglutination was comparable to agglutination of the patient's mature erythrocytes.

Role of the Spleen.—Table 4 represents data on comparative studies performed on blood removed from the splenic artery, splenic vein, and splenic pulp. There was no

TABLE 4.—*Comparison of Various Laboratory Values in Blood from Splenic Artery, Splenic Vein, and Splenic Pulp*

	Splenic Artery	Splenic Vein	Splenic Pulp
Antiglobulin test	4+	3+	3+
Titer	256	256	128
Isoagglutinins			
Saline			
3 C	16	32	16
20 C	1	1	1
37 C	1	2	1
Trypsin			
3 C	128	128	128
20 C	16	16	16
37 C	16	8	8
Hemolysins	0	0	0
Mechanical Fragil.	26.5%	32.4%	—
Inagglut.-Cell-Count	840,000	875,000	—
Bilirubin, mg. %	13	17	10

TABLE 5.—*Red Cell Agglutinins Eluted from Tissues Removed at Autopsy*

	Marrow		Spleen		Kidney		Lung		Liver		Adrenal	
Titer	3 C*	56 C*	3 C*	56 C*	3 C*	56 C*	3 C*	56 C*	3 C*	56 C*	3 C*	56 C*
1:1	0	2+	±	2+	1+	1+	2+	2+	1+	2+	2+	1+
2	0	1+	0	2+	1+	1+	2+	1+	1+	2+	1+	±
4	0	0	0	1+	1+	1+	1+	1+	1+	1+	0	0
8	0	0	0	1+	±	1+	1+	1+	±	0	0	0
16	0	0	0	1+	0	±	0	±	0	0	0	0
32	0	0	0	1+	0	±	0	0	0	0	0	0
64	0	0	0	±	0	0	0	0	0	0	0	0
128	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0

* Agglutination of trypsinized Type O Rh-negative RBC versus tissue eluates (I. B.) at 37 C.

difference in the titer of antiglobulin test, in the titer of autoantibodies, and in agglutinable-cell count in blood obtained from the splenic artery, vein, and pulp. However, the mechanical fragility of splenic-vein blood was slightly higher than that of the artery. Also, the amount of bilirubin in the splenic-vein blood exceeded that in the splenic artery blood.

Attempt to Demonstrate Tissue Antibodies.—An attempt was made to isolate a hemagglutinin or hemolysin from the postmortem tissues. Finely minced pieces of organs were frozen in liquid nitrogen, ground with a laboratory mill, and then freeze-dried over a vacuum-suction apparatus; 50 mg. fragments of each organ were suspended in 1.0 ml. of saline. One portion was incubated for 12 hours at 3 C. Another portion was incubated for two hours at 56 C. The supernatant fluid thus obtained was diluted serially with isotonic saline; a 3% suspension of trypsinized Group O erythrocytes was added, and the systems were incubated at 37 C for four hours and then read for agglutination. The results of this experiment are listed in Table 5. An agglutinin could be isolated from the various tissues by elution at 56 C and, to a much smaller degree, by elution at 3 C. This tissue agglutinin was demonstrated by comparative titer to be demonstrable in greatest dilution in splenic 37 C saline eluates.

When normal erythrocytes were incubated together with tissue eluates, the antiglobulin test became positive. The strongest (2+) antiglobulin test was derived from a mixture of lyophilized spleen with normal erythrocytes.

Hemolytic activity was not present when the above eluates were incubated with complement and normal erythrocytes.

Comment

The clinical picture of autoimmune hemolytic anemia may be variable. At one extreme, there may be evidence of autosensitization without incapacitation. Young and Miller [8] presented a study of the long term course of 23 patients with autoimmune hemolytic disease in which 9 patients did not require treatment with corticosteroids despite a positive antiglobulin reaction. Rosenthal, Komninos, and Dameshek [9] presented a remarkable patient with multiple antibodies and with fairly low erythrocyte values who apparently tolerated her degree of anemia very well. On the other hand, most patients with autoimmune hemolytic anemia require constant attention, because unpredictable clinical relapse and precipitous drops in the red cell count are a danger whenever autoantibodies can be demonstrated. The patient reported herein is an example of constantly severe hemolytic disease.

The factors which underlie clinical severity in autoimmune hemolytic disease are multiple and for the most part poorly understood. Contributing to severity are a possible etiologic factor, the type and specificity of autoantibodies, and the degree to which erythrocytes may be sensitized.

The etiologic factor is an important determinant of the clinical pattern, as there are some diseases associated with autoimmune hemolytic anemia which in themselves may result in considerable morbidity. For example, disseminated lupus erythematosus, even without complicating hemolytic anemia, may result in violent signs and symptoms. In the patient under discussion, a definite etiologic disorder was not found, but there was evidence that this disease began with an infection; pneumonitis was present before a history of anemia was obtained and shortly after the first hospital admission. The course during the first relapse was febrile, and the patient finally succumbed to an infectious process masked by the corticosteroids. Of possible importance was the history of exposure to brucellosis, which developed in a companion at work. Repeated blood cultures and agglutination studies failed to disclose any evidence of Brucella or any other organism in our patient. The possible relationship of viruses to development of autosensitization of erythrocytes has received considerable attention since Moolten's isolation of the Newcastle disease virus from his case.[10]

The presence in our patient of an antibody against the mumps virus in fairly substantial titer may be of interest, but he did not have clinical mumps. It cannot be stated that a specific virus caused infection in this patient because a live virus was not isolated from his serum and secretions.

In most cases, the presence of autoantibodies is a prerequisite to the development of the hemolytic syndrome in autoimmune hemolytic anemia. However, the quantitative relationship between red cell autoantibodies and the viability of the erythrocyte in vivo has yet to be defined, as an exact method to estimate quantity of antibody is not yet available.

Antibody is commonly estimated by determining the score of the highest dilution of patient's or of antiglobulin serums at which agglutination of erythrocytes will occur and by the size of the erythrocyte aggregates from 1 to 4+. Dameshek[11] has suggested a very rough correlation between titratable amount of antibody in the serum and red cell life span. Evans and Duane[12] assayed the amount of antibody attached to erythrocytes by diluting antiglobulin serum serially and found a similar correlation between amounts of antibody and activity of the disease. More recent studies by Fudenberg, Barry, and Dameshek[13] confirmed these observations by measuring protein eluted from erythrocytes by a micro-Kjeldahl technique. Our observations confirm the above studies in that a strongly positive antiglobulin test was constantly present for the entire course of our patient's illness.

Interpretation of the significance of a positive Coombs antiglobulin reaction has been the subject of discussion. Strictly interpreted, the antiglobulin test demonstrates the presence of serum proteins on the surface of erythrocytes. A positive antiglobulin test need not necessarily signify an immunologic reaction, as proteins can attach themselves to erythrocytes previously damaged by various substances, such as heavy metals.[14] However, this "protective" coating of erythrocytes usually involves all fractions of the serum proteins, while in the "immunologic" variety of antiglobulin reaction, it is only the γ-globulin fractions which coat the erythrocyte.[6] If the proteins eluted from an affected erythrocyte show serologic specificity, selectively directed against a certain red cell antigen, we may consider the antiglobulin reaction to be an immunologic one. If the eluted antibody shows activity only against an agglutinogen contained in the patient's own erythrocytes, an autoantibody is said to be present.[15] Most frequently, as experienced in the present patient, the eluted protein will agglutinate or sensitize all erythrocytes, regardless of serologic specificity. Some of these nonspecific panagglutinins are said to be related to the basic nucleus of the Rh agglutinin.[16] The γ-globulin nature of many of these erythrocyte-coating substances has been adequately demonstrated[16-18] with finality, including the erythrocyte-coating substance of the patient under discussion. While not all

γ-globulins are antibodies, the intense affinity of panagglutinins derived from γ-globulin for erythrocytes of all types, and which resists repeated attempts to be washed off, suggests a specific relationship between the protein and the red cell, similar to an antigen-antibody reaction. Further evidence for the antibody nature of the erythrocyte-coating protein in this patient may be found in the affinity of the patient's proteins for normal erythrocytes but lack of similar affinity of a normal person's serum globulin for the patient's erythrocytes. Mollison [19] has clearly demonstrated that the transfusion of normal red cells into a patient with autoimmune hemolytic disease results in their rapid exponential destrucion; whereas the transfusion of erythrocytes from a patient with autoimmune hemolytic anemia into a normal results in a normal, linear survival time. In our present study, we have performed an Ashby survival study, using antiglobulin serum as agglutinating agent (Fig. 4), and have shown that normal erythrocytes become coated with the patient's protein within 24 hours after they are infused. It would be desirable to know whether γ-globulin derived from normal humans would have an affinity for red cells in vivo in patients with a positive antiglobulin test. In another study,[20] normal human γ-globulin, labeled with I^{131} was given intravenously to a patient with autoimmune hemolytic anemia and whose erythrocytes were coated with γ-globulin. Radioactive red cells did not result, suggesting that normal human γ-globulin had no affinity for this patient's erythrocytes. These in vivo studies demonstrate the affinity of γ-globulin from patients with autoimmune hemolytic anemia for all erythrocytes. On the other hand, the lack of affinity of normal γ-globulin for antiglobulin positive erythrocytes is strong evidence that in autoimmune hemolytic anemia the Coombs reaction depends upon a specific relationship between patients' globulin and all erythrocytes.

Nonhemolytic or agglutinating antibodies act in some way by limiting the life span of the red cell. That they also limit bone marrow response to hemolysis was shown when normoblasts derived from the patient's blood were agglutinated by antiglobulin serum and by autoagglutinin.[7] Hemagglutinins may also alter the physical properties of erythrocytes. There is frequently an increase in mechanical fragility, which implies that a red cell subjected to the trauma of circulation might become destroyed intravascularly. This may not be clinically significant because of the relatively low incidence of intravascular hemolysis in autoimmune hemolytic disease during quiescent periods. However, the frequent occurrence of spherocytosis in autoimmune hemolytic disease provides an excellent explanation for early destruction of red cells. Spherocytes are likely to occur following damage with anti-A agglutinins and with high titers of autohemagglutinins. Perfusion experiments [21] and, more recently, studies with C^{51}-labeled erythrocytes [22] show that destruction of spherocytes is frequently accomplished by selective sequestration in the spleen and other reticulonendothelial tissues.

A direct explanation for hemolysis in immunologic hemolytic anemia would be the demonstration of hemolytic antibodies. However, hemolysins are rarely demonstrated in vitro, but in our patient were almost constantly present in his serum and also on the surface of his washed erythrocytes. The presence of these antibodies in part explains the peculiar severity of this patient's illness.

The role of the spleen in hemolytic disease seems to center about two functions: (1) as antibody producer and (2) as a sequestering agent for damaged red cells. In the data shown on Table 4, there was no difference in the antibody titers and in agglutinable-cell counts of splenic artery and vein. We have no explanation for the variance between this observation, and other studies which show clearly that there is specific splenic sequestration of C^{51}-labeled erythrocytes in hemolytic disease. Splenic sequestration may be a consequence of the spherocytic shape, which prevents reentry of the spherocyte into the circulation or, as Jandl [23] has more recently suggested, that

agglutinated groups of erythrocytes and reticulocytes may not be able to escape into the circulation through narrow sinusoidal openings. The actual events that precede splenic destruction are likewise in doubt. There is evidence that sequestered red cells might be chemically altered and deprived of the protective effect of their intrinsic glyolytic metabolism, which is said to provide the erythrocyte with high-energy phosphate bonds.[24] In the absence of this protection, the erythrocyte loses potassium, gains sodium and water, and then ruptures. The alternate hypothesis, that tissue hemolysins exist, has been tested by crude methods in our laboratory. Exposure of fresh and trypsinized normal erythrocytes to mixtures of autopsy tissue extracts, and complement (Table 5) failed to cause hemolysis. In a similar study, Wagley and co-workers[25] showed than an erythrocyte-coating protein could be derived from spleens from autoimmune hemolytic anemia. It appears from our data that the spleen is the source of antibody in highest dilutions when compared to extracts from other organs. However, it is more likely that these agglutinins were derived from peripheral blood trapped in this organ, as the spleen is extremely rich in vascular tissue and contains a larger amount of peripheral blood than the other organs.

The hematologic values in the patient exemplify a severe degree of hemolytic anemia, spherocytosis, and an attempt at compensation by the bone marrow. Hemolytic episodes were attended by evidences of erythrophagocytosis in direct smears (Fig. 1). On occasion, leukophagocytosis and thrombophagocytosis were also seen. Reticulocytosis was constant, but response to corticosteroids or a hemolytic crisis was associated with an even greater increase in the number of reticulocytes, at times as high as 68%. These were accompanied by periodic release of large numbers of nucleated red cells into the peripheral blood. Normoblasts were noted to show various degenerative changes, notably nuclear karyorrhexis.

For the entire clinical course, moderate leukocytosis was the rule during periods of active hemolysis. However, in those phases where hemolysis was controlled, a tendency toward leukopenia was noted in that the leukocytes hovered around 3 to 6,000 per cubic millimeter. The platelets showed a similar tendency toward thrombocytopenia, and for the major part of the course, a platelet count under 100,000 was noted. After splenectomy, the leukocyte and platelet counts increased to a peak of 37,000 and 447,000 per cubic millimeter. Shortly before death, the extreme leukocytosis was an expression of the terminal subdiaphragmatic abscess.

Absence of leukagglutinins and platelet agglutinins during the leukopenic and thrombopenic phases of this illness, plus the return of the leukocyte and platelet counts to high levels after splenectomy, suggested that leukopenia and thrombopenia were secondary to the inhibiting effect of a large spleen. However, we cannot rule out Evans' contention[26] that erythrocytes, platelets, and leukocytes were attacked by a common antibody.

Summary and Conclusions

The case study has been presented of a 38-year-old Negro man with an extremely severe form of autoimmune hemolytic anemia.

The illness began with a febrile episode. Although the patient was actively exposed to brucellosis and showed antibodies to the mumps virus, a bacterial or virus etiology could not be proved.

The severe hemolytic disease was accompanied by a strongly positive Coombs antiglobulin test and by an erythrocytic panagglutinin in the serum with activity against all human erythrocytes, including those of the patient. A hemolysin was also found in the serum and attached to the surface of the erythrocyte, which could also account for the severity of this man's illness.

Normal erythrocytes introduced into the patient, became coated with the patient's

protein within 24 hours, and disappeared from the circulation 24 hours later.

There was no difference in titer of erythrocyte antibodies, inagglutinable-cell count and titer of antiglobulin reaction of blood from the splenic artery, vein, and pulp. However, splenic vein blood showed a greater mechanical fragility and increased concentration of bilirubin.

Normoblasts, isolated from the patient's circulation during a hemolytic crisis, were agglutinated by type-specific antiserum, by antiglobulin serum, and by serum containing autohemagglutinins. This demonstrates the existence of immunologic receptors in developing normoblasts and implies that the bone marrow is under attack in autoimmune hemolytic anemia.

Treatment with corticosteroids showed a limited response. Splenectomy had no effect upon antibody production or on the hemolytic anemia.

Red cell agglutinating and sensitizing substances were extracted from the tissues removed at autopsy. These were likely derived from peripheral blood trapped in the tissues.

The following physicians of the Milwaukee County General Hospital participated in the care of this patient: Drs. William V. Baker, Louis R. Jermain, James V. Pilliod, Edward J. Brucker, James L. McKenna, and John J. Smith.

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Digitalis-Induced Ventricular Fibrillation

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In 1951, Enselberg and associates reviewed the literature pertaining to digitalis-induced ventricular fibrillation.[1] Only four well-documented cases with electrocardiographic substantiation were found. To these the authors added two cases of their own. Both were due to intravenously administered acetylstrophanthidin. In 1953, Burrell and Coggins reported another patient with acetylstrophanthidin-induced ventricular fibrillation,[2] bringing the number of cases to a total of seven.[1-3] In most of these patients ventricular fibrillation was rapidly fatal.[1,2] The purpose of the present communication is to report a patient who recovered from digitalis-induced ventricular fibrillation which lasted intermittently for over four hours.

Report of Case

A 41-year-old white woman with advanced disseminated lupus erythematosus was admitted to the hospital on May 6, 1957. The diagnosis of lupus erythematosus had been made in 1953. Congestive heart failure appeared in January, 1956. There was no known antecedent heart disease.

On examination the patient was orthopneic with shallow, labored breathing. She showed marked cachexia, generalized edema, pulmonary congestion, and bilateral pleural effusion. The heart was moderately enlarged. There was a Grade 2 to 3 systolic apical murmur, a ventricular rate of 100, and diastolic gallop rhythm. The blood pressure was 180/100. The optic fundi were normal except for cytoid bodies. The liver extended 6 cm. below the costal margin.

Laboratory Data.—Urinalysis: specific gravity 1.016, albumin 3+, 6-8 granular casts per high-power field. The hematocrit was 34 mm. The BUN was 25 mg. %. Serum albumin was 2.3 gm. % and globulin 4.7 gm. %. The L. E. preparation was positive. Carbon dioxide-combining power was 17.2 mEq. per liter. Serum sodium and potassium were within normal limits.

There was uncertainty as to the medications that the patient had been taking prior to hospitalization. She had required digitalis in the past (preparation unknown) but had not taken any for the preceding several days.

The electrocardiogram on admission showed sinus tachycardia with a ventricular rate of 100 and nonspecific ST and T changes (Fig. 1, ECG Strip 1). She was given 0.3 gm. of digitalis leaf orally and 1 cc. of meralluride (Mercuhydrin) intravenously. The following day (May 7) she received intravenously 0.4 mg. of lanatoside C, at 11 a. m. and 3 p. m., and 2 cc. of meralluride. Corticoids were started and continued daily. No potassium chloride was given until May 8.

During the evening of May 7, an emergency tracheotomy was performed because of difficulty with secretions, and by 9 p. m. there appeared to be some improvement. An electrocardiogram at that time showed an atrial tachycardia, with 2:1 A-V block (Fig. 1, ECG Strip 1*a*). Unfortunately, the arrhythmia was not recognized as consistent with digitalis toxicity, and 0.2 mg. of lanatoside C was given, at 9 p. m. and at 11 p. m.

One hour and forty-five minutes after the 11 p. m. dose the patient suddenly developed "tremor" and became cyanotic and unresponsive. No heart sounds could be heard, and the blood pressure was unobtainable. Vigorous pounding over the precordium was followed by rare heart beats. The pounding over the precordium was continued for the next hour, and oxygen was administered by a resuscitator through the tracheotomy tube. The heart sounds were described as "rare heart beats or very short runs of beats followed by long intervals of silence."

At 2:05 a. m. an electrocardiogram was obtained (Fig. 1, continuous ECG Strips 2 and 3). It showed, in succession, ventricular fibrillation, idioventricular complexes, and ventricular tachycardia. At this point 100 mg. of procainamide (Pronestyl) was given intravenously (Fig. 1, continuous ECG Strips 3 and 4). During the next five minutes the tracing showed ventricular fibrillation (Fig. 1, ECG Strip 4), then rather infrequent idioventricular complexes, runs of ventricular tachycardia, and again ventricular fibrillation (Fig. 1, continuous ECG Strips 5-9). At 2:10 a. m. another 100 mg. of procainamide was given intravenously (Fig. 1,

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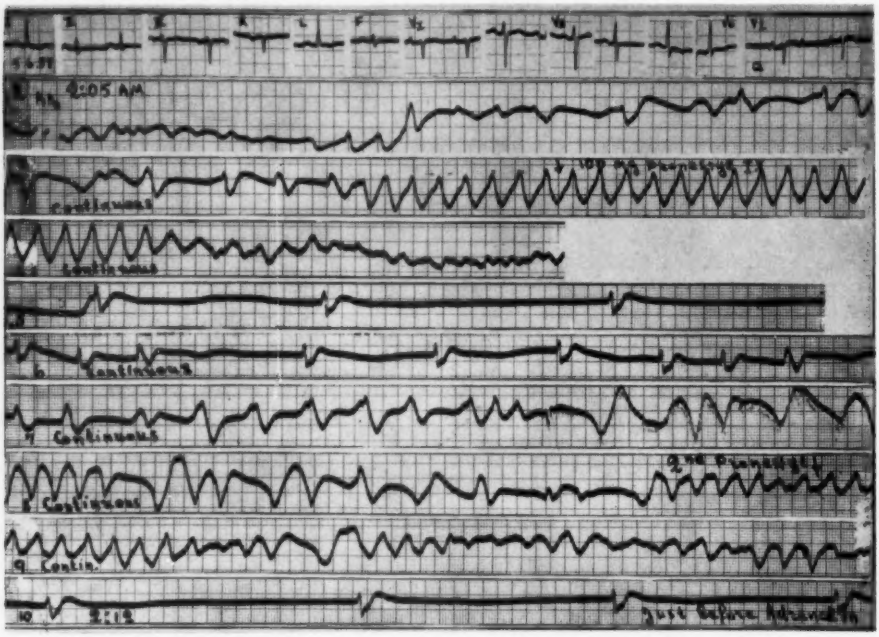
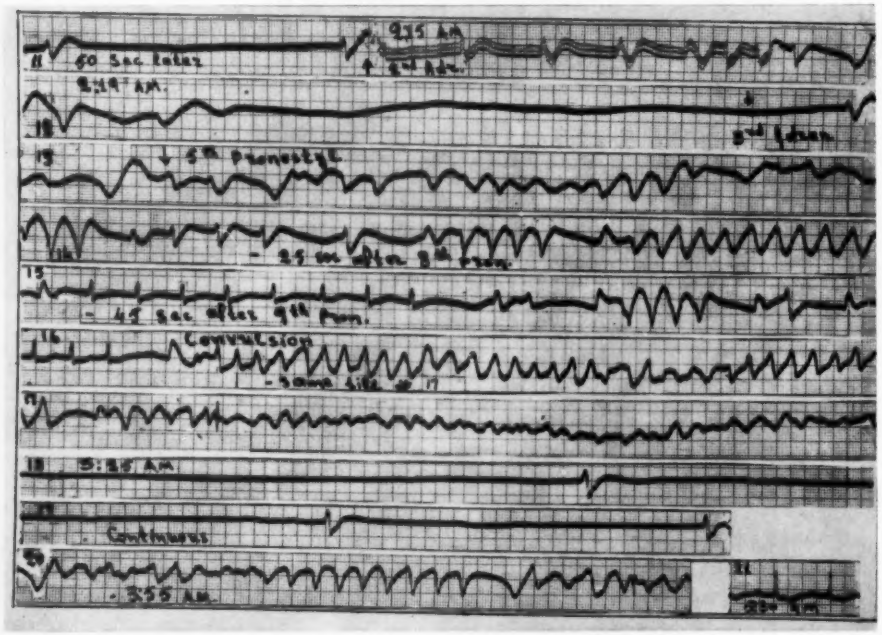


Fig. 1.—Twelve-lead admission electrocardiogram is shown at the top, followed by V_1, taken on May 7, 1957. Other strips are described in text. Strips 2-4 and 5-9 are continuous.

Fig. 2.—Strips are described in text.



ECG Strips 8 and 9). For the following two and one-half minutes ventricular fibrillation alternated with ventricular tachycardia (ECG not shown) and was succeeded by a slow idioventricular rhythm (Fig. 1, ECG Strip 10). After administration of 1 mg. of aqueous epinephrine 1:1,000 intravenously, the idioventricular rate increased but was followed by ventricular fibrillation (ECG not shown). The third 100 mg. of intravenous procainamide was given, and 50 seconds later idioventricular complexes reappeared (Fig. 2, ECG Strip 11). A second 1 mg. of epinephrine was given. The ventricular rate increased, only to be followed by ventricular fibrillation (ECG not shown) and then by a period of asystole lasting eight to nine seconds (Fig. 2, ECG Strip 12). At this point a third 1 mg. dose of epinephrine was given intravenously. The chain of events appeared to repeat itself: epinephrine speeding up the ventricular rate, with ventricular fibrillation supervening and procainamide aborting ventricular fibrillation, followed by idioventricular complexes and runs of ventricular tachycardia (Fig. 2, ECG Strips 12, 13, and 14).

Between 2:05 a. m. and 3:00 a. m. the patient received intravenously a total of 900 mg. of procainamide and 3 mg. of epinephrine. Potassium chloride was not given because it was not recognized at the time that the arrhythmia was due to digitalis.

At 2:40 a. m. and again at 3:15 a. m. there was a brief phase of supraventricular rhythm (Fig. 2, ECG Strips 15 and 16), and at 3:00 a. m. the patient responded for a short period of time. However, between 3:00 a. m. and 5:30 a. m. the patient had several convulsive episodes, the electrocardiogram revealing ventricular tachycardia, ventricular fibrillation, and rare idioventricular beats with long periods of asystole (Fig. 2), ECG Strips 16-20; 18 and 19 are continuous). Repeated pounding over the precordium was resorted to. Oxygen was continued by resuscitator. No additional drugs were given because the situation seemed hopeless.

From 2:05 a. m. until 5:30 a. m. electrocardiographic tracings were taken repeatedly. During this period there were several runs of ventricular fibrillation lasting up to five minutes, and again, in each instance in desperation, pounding over the the precordium was resorted to.

Suddenly at 5:30 a. m., some four hours after the onset of the arrhythmia, sinus rhythm appeared with first-degree A-V block and a ventricular rate of 78 per minute (Fig. 2, ECG Strip 21). The blood pressure was 170/80. At 5:45 a. m. the patient responded and attempted to say a few words.

At 8:30 a. m. the electrocardiogram was essentially the same but the ventricular rate had increased to 107 per minute. The patient's sensorium appeared unchanged from that prior to the events of the night. The neurologic examination was negative. There was no oliguria.

Because of the increasing tachycardia and dyspnea digoxin was given intravenously at noon (0.25 mg.) of the same day and that night (0.125 mg.), with some improvement in the patient's condition. She also received 2 cc. of meralluride. The following day (May 9, 1957) the electrocardiogram revealed A-V dissociation, with frequent premature ventricular contractions (tracing not shown). These were corrected by the omission of digoxin and the administration of potassium chloride.

During the next several days the patient showed steady improvement. However, this was soon followed by clinical deterioration, characterized by increasing prostration, fever, and rapidly rising blood urea nitrogen (40 mg. % on May 8, 1957, to 155 mg. % on May 16) with electrolyte derangement. The patient was continued on steroids, potassium chloride, and small amounts of digoxin. She died on May 19, 1957, eleven and one-half days after the digitalis-induced ventricular fibrillation, in shock with a bizarre arrhythmia similar to that of May 7, 1957 (electrocardiogram not shown). The same therapeutic measures were employed, but without success. Permission for postmortem examination was denied.

Summary

A case of disseminated lupus erythematosus with congestive heart failure and ventricular fibrillation attributed to digitalis toxicity is reported. Its forerunner was an atrial tachycardia with a 2:1 A-V block, and it is reemphasized that its development in any patient taking digitalis is an indication of digitalis toxicity. Ventricular fibrillation was present intermittently for over four hours. Several runs of ventricular fibrillation were recorded, lasting up to five minutes at a time. The patient survived this episode without demonstrable central nervous system changes and lived for 11½ days. To the best of our knowledge, this is the first such case on record.

Dr. John M. Evans and Dr. Clayton B. Ethridge helped in the preparation of this report and Mr. P. Sourori, fourth year medical student, gave professional aid.

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Ventricular Fibrillation Due to Myocardial Infarction with Survival

Report of a Case in a Patient with Hemochromatosis and Panhypopituitarism

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The advent of widespread experimental and clinical experience in the fields of thoracic and cardiovascular surgery has produced an increasing awareness and knowledge concerning the recognition and treatment of ventricular fibrillation.* In recent years, several reports [7,16,32,36] have indicated that this information has been utilized in the treatment of ventricular fibrillation complicating acute myocardial infarction. There have been three previous reports wherein long-term survival has been recorded after successful treatment.

Beck [7] recorded the first case, in 1955; the second, also reported in 1955, was that of Celio,[16] and the third was that of Reagan,[36] in 1956. Data relative to these three cases and the fourth, which we are presenting, are tabulated in the Table. All four patients had sudden onset of pain: in the first it was located only in the precordium; in the second, both abdominally and substernally, and in the third it was substernal and radiated to both arms. In one of these patients an electrocardiogram was obtained prior to the onset of symptomatology referable to the present illness. Changes in the electrocardiograms taken at or after the onset of the presenting complaint of pain were compatible with a diagnosis of anterior wall myocardial infection. The present case is unusual in that an electrocardiogram taken prior to the onset of any symptoms referable to the cardiovascular system was available for comparison (Fig. 1). In the case reported by Reagan, the etiology of the cardiac disturbance was revealed by the appearance of a ventricular fibrillation pattern in Lead V_2, whereas the diagnoses in the patients reported by Beck and Celio were made when the chest was opened.

Evidence of preexisting chronic disease was present in two of the previous cases. In those reported by Beck and Celio, symptomatology which may have been attributable to the cardiovascular system had been noted prior to the onset of the episode of acute pain. These complaints of acute pain were seemingly most indicative of coronary artery disease in Beck's and Reagan's patients and in our own. However, since our patient had proven idiopathic hemochromatosis of 11 years' duration, there were many additional unique factors influencing the initial diagnosis [17,27,40] and his course after the diagnosis was established and initial treatment instituted.

Report of Case

This was the sixth admission of this patient, a 51-year-old white male chemist, who entered via the emergency room, complaining of left-sided severe chest pain of one hour's duration. The patient had had the diagnosis of idiopathic hemochromatosis established with the aid of liver biopsy in 1946 at another hospital. Since that time, polyglandular insufficiency had developed, the patient having been discharged from this hospital only three days previously after reevaluation of his metahormonal therapy.

One hour prior to admission, while awaiting dinner, the patient had experienced the sudden onset of severe, crushing, left anterior chest pain, radiating to the left shoulder and down the medial

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*References 5-8, 13, 14, 21, 29, 30, 34, 38, 39, 41, 42, 44, 48.

Cases of Ventricular Fibrillation Complicating Acute Myocardial Infarction

Author	Sex	Age	Occupation	Previous Vascular Disease	Associated Disease	Time to Definitive Treatment, Min.	Duration of Survival	Mental Status	Method of Diagnosis
Beck[7]	M	65	Physician	Coronary artery disease manifest by angina pectoris	None noted	5	Well as of Sept. 1956	Amnesia for 36 hr. after onset of fibrillation	Direct vision
Cello[10]	M	46	Carpenter	Chest pain after strenuous exertion 24 yr. previously, followed by dyspnea & occasional precordial pain with exercise	Duodenal ulcer	2-3	Well at 3-mo follow-up	Amnesia for events of day of fibrillation	Direct vision
Reagan[14]	M	55	Truck driver	None noted	None noted	1	Well as of Dec. 1955	Amnesia for 24 hr. after onset of fibrillation	ECG V_5
Conklin et al.	M	51	Chemist	Anginal syndrome about 1 mo.	Hemochromatosis 11 yr., with diabetes, hypopituitarism, hypoandrogenism, hypothyroidism, hypoadrenocorticism	4 ½	Well at 9-mo. follow-up	Amnesia for 5 days following fibrillation; slight impairment of distant recall	ECG V_6

aspect of the left arm. His physician administered 250 mg. of meperidine hydrochloride parenterally to control this pain while he awaited transfer by ambulance to the hospital. Prior to transfer, the patient's blood pressure was 140/90; pulse, 110 and regular; no diaphoresis, nausea, or vomiting was noted.

On admission to hospital, the blood pressure was 110/70; pulse, 72 and regular, and respirations, 18 and somewhat shallow. The patient was observed to be in acute distress with persistent chest pain and to be pallid despite his generally increased pigmentation. The pupils were pinpoint size but equally reactive. There was no neck vein distention; the thyroid gland was smooth, symmetrically enlarged, and estimated to weigh about 40 gm.; no bruit was noted. The lungs were clear to percussion and auscultation. The heart was not enlarged; no thrill was palpable; the sounds were soft, with a regular rhythm. $M_2 > M_1$; $A_2 = P_2$, and no murmurs were audible.

The abdomen was soft; the liver was palpable 5 cm. below the right costal margin and firm, smooth, and nontender. No other palpable organs or masses were noted, and peristalsis was hypoactive. The extremities demonstrated increased extensor pigmentation of a slate-brown hue; all pulses were equally palpable, and no edema was noted. The neurological examination was within normal limits.

Hospital Course.—During the recording of an electrocardiogram after completion of the physical examination, the pattern of ventricular fibrillation appeared while Lead V_4 was being recorded. The patient became intensely cyanotic, with four respirations per minute and without discernible pulse or blood pressure. An oral airway was immediately inserted, a face mask applied, and chest-compression artificial respiration instituted. A left thoracotomy was accomplished four and one-half minutes after the onset of fibrillation, with the aid of the surgical house staff, and cardiac massage begun. An endotracheal tube was inserted by the anesthesiology service, and oxygenation with 100% oxygen begun. A tracheostomy was later performed.

After 15 minutes with no response to massage or intracardiac epinephrine, electrical defibrillation was accomplished on the second attempt. Asystole was followed by a brief period of normal sinus rhythm, then an idioventricular rhythm, and then reversion to normal sinus rhythm. After the addition of norepinephrine (arterenol) to the intravenous infusion, the peripheral blood pressure became obtainable and was maintained at 90 to 110 mm. During the initial treatment period, the patient received hydrocortisone, tetracycline, diphenylhydantoin sodium, quinidine hydrochloride, and regular and isophane (NPH) insulin. Anticoagulation was instituted 12 hours after admission,

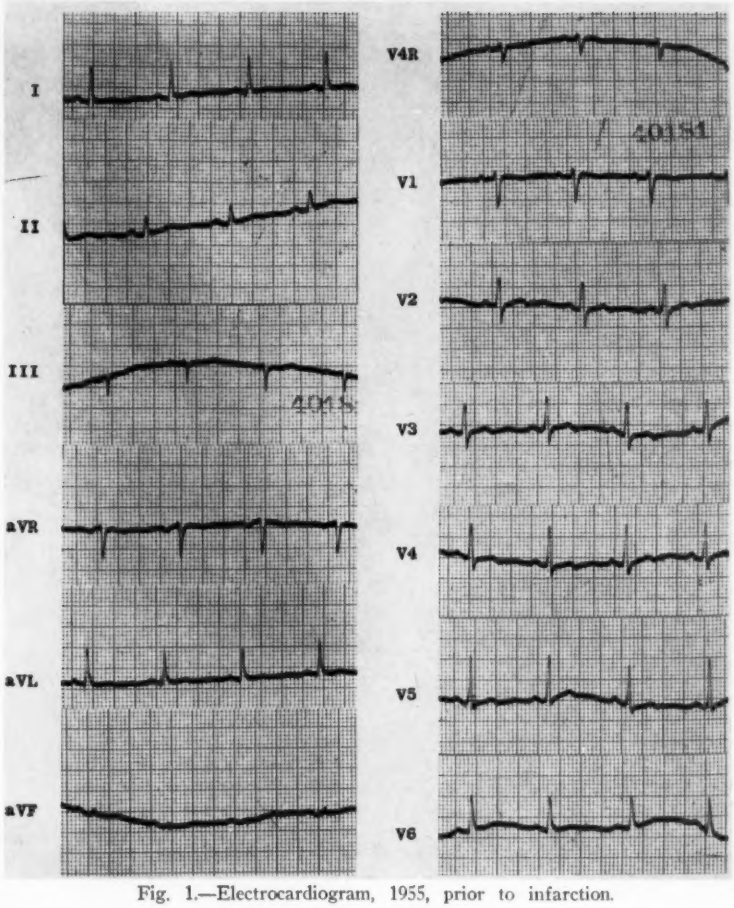

Fig. 1.—Electrocardiogram, 1955, prior to infarction.

with use of aqueous heparin sodium parenterally, and when the patient was able to take oral medication, warfarin (Prothromadin) sodium was substituted.

During the first 24 hours, the patient was extremely restless but his vital signs remained relatively stable. On the second day, he was able to recognize and follow directions but did not attempt to speak. On the third day, the tracheostomy tube was plugged and the chest catheter removed; the patient was able to whisper a few words and take fluids orally. On the fourth day, the temperature rose to 104 F and diminished resonance was apparent at the left lung base. There was a small amount of purulent drainage from the operative site, which on culture was demonstrated to be hemolytic Staphylococcus, coagulase positive. On the fifth day, the patient had several diarrheal stools, which yielded a Gram-negative bacillus overgrown with Proteus on culture. There was evidence of bilateral basilar consolidation on examination of the chest. Portable chest x-ray demonstrated a region of consolidation in the right lower lung field. Tetracycline was discontinued and erythromycin started.

The postinfarction course was further complication by a Candida albicans stomatitis, hypoproteinemia, electrolyte imbalance, and a superficial wound infection. These gradually resolved under careful management. Electrocardiographic demonstration of resolution of the anterior wall myocardial infarction is seen in Figures 2, 3, 4, and 5, a stable pattern being present by the 24th postinfarction day. At this point the patient had been returned to the hormonal maintenance levels utilized prior to infarction: cortisone, 25 mg. daily; isophane insulin, 40 units daily, and thyroid extract, 15 mg. daily. Owing to the per-

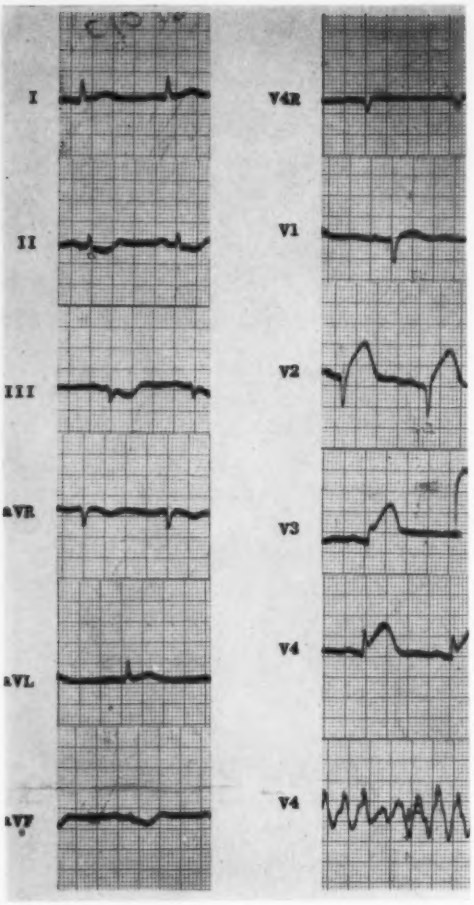

Fig. 2—Electrocardiogram, on admission, with ventricular fibrillation pattern in Lead V_4.

sistent hypoproteinemia, norethandrolone, 40 mg. daily, was instituted and a liberal salt intake was provided.

There was gradual improvement, and the patient was discharged home on the 41st hospital day to continue rest and progressive ambulation. Apart from amnesia for the first five hospital days and a slight impairment in distant recall, there is not a detectable change in the patient's mental prowess. He returned to full employment and seven months postinfarction underwent an excisional biopsy of a breast nodule under general anesthesia without incident.

Comment

A multitude of factors believed to contribute to the development of coronary atherosclerosis have been presented by many investigators.† In this patient, both diabetes mellitus and hypothyroidism had been diagnosed. There is ample evidence ‡ that both diabetes and hypothyroidism predispose to earlier appearance, more diffuse involvement, and increased mortality from coronary artery disease than that experienced in the general population. Bartels and Bell [4] reported that in 59 cases of hypothyroidism one-third of the patients having the disease for two years without treatment exhibited coronary artery disease and all patients with the disease for five years had coronary artery disease.

† References 4, 18, 19, 21, 22, 24, 25, 28, 37.
‡ References 4, 17-19, 21, 22, 24, 28, 37.

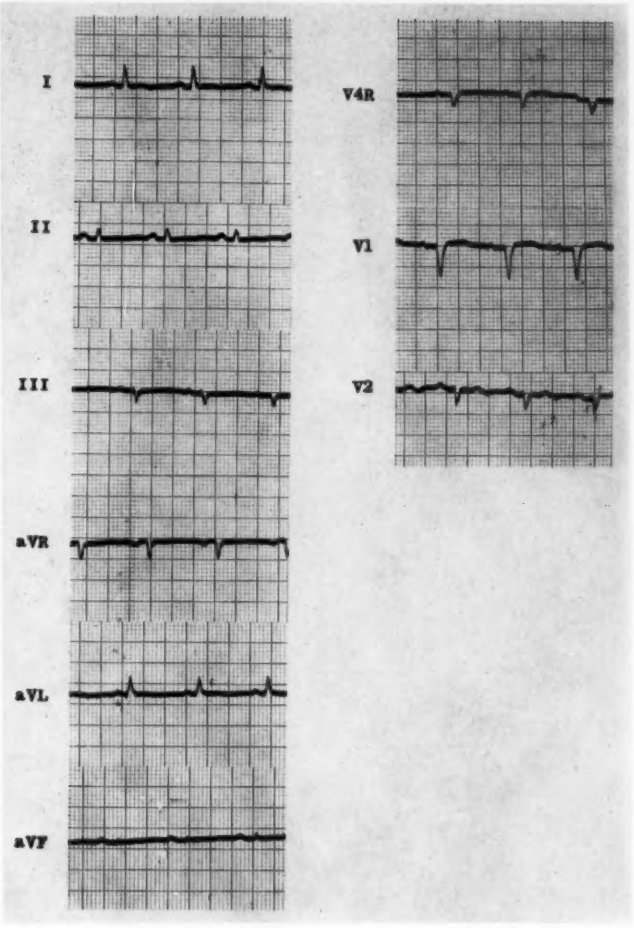

Fig. 3.—Electrocardiogram seven days after infarction.

Further complexity is afforded by the 11-year history of hemochromatosis present in this patient. Specific information pertaining to the incidence of coronary atherosclerosis in patients with hemochromatosis relative to other populations is not available, but cardiovascular symptomatology does occur.§ Finch and Finch, in their review of the world literature, conclude that about 33% of patients with hemochromatosis develop congestive heart failure in the course of their disease and about the same proportion eventually die of the cardiac manifestations of their disease. This is in contrast to Sheldon's review published 20 years earlier and also at variance with that reported by many French investigators, who found a high incidence of cardiovascular complications manifest early in the course of the disease.

Pathologic lesions of the cardiovascular system have been variously described, only perinuclear deposition of hemosiderin having been observed in some instances, while in others there has also been noted myocardial degeneration and fibrous replacement.[1,10-12,20] Comparison of the patients' symptomatology with electrocardiographic findings, with the incidence of congestive heart failure, and

§ References 1, 9-12, 17, 20, 26, 27, 31, 33, 40.

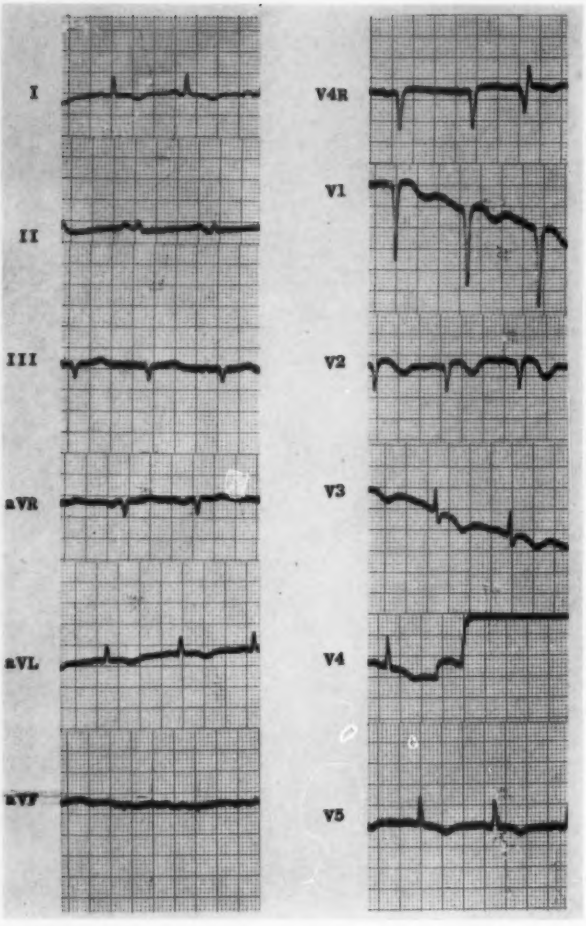

Fig. 4.—Electrocardiogram, at discharge, 41 days after infarction.

with pathologic findings post mortem have failed to yield any information of note.

The direct myocardial effects of the many therapeutic agents used in this case have been studied only in part. In most instances, the effect of only a single drug administered at one time has been described; in very few have simultaneous combinations of drugs been studied. Little assistance in attempting to evaluate the possible contribution to survival of the drugs used could be obtained from literature. Adrenocortical hormones have been reported to inhibit fibroblastic activity [35] and deter wound healing.[2] Direct toxic effects on the myocardium have been noted,[15] yet they have been utilized in the treatment of cardiac arrhythmias due to myocardial infarction with success.[34]

Insofar as could be ascertained by serial electrocardiographic study, no delay in the resolution of the myocardial infarction was evident in this patient. The recent observations of Barrie and Urback [3] concerning the cellular changes in healing myocardial infarction may offer a possible explanation for this finding.

The effects of the many drugs utilized in treatment in this case on the central nervous system are even less well understood.[46,47] As indicated in the Table, it would appear that hypoxia was more profound in the

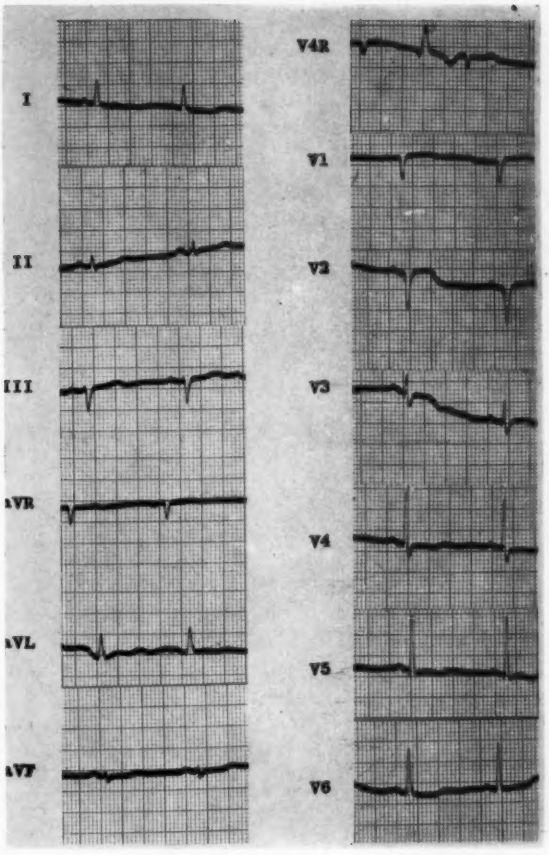

Fig. 5.—Electrocardiogram nine months after infarction.

present case or present for a longer time, as evidenced by the prolonged amnesic period and the residual minimal lack of distant recall. Aside from the control of infection, the only therapeutic effect of possible significance in this patient was the deliberate maintenence of a hypometabolic state through suboptimal doses of thyroid extract and cortisone, possibly permitting a diminution in cardiac work in the postinfarction period.

From information presented in the literature and our experience with this and other cases of cardiac arrest associated with operative procedures, we have reached the following tenative conclusions:

1. Ventricular fibrillation complicating acute myocardial infarction can be treated successfully. It requires a definitive diagnosis by electrocardiogram, availability within three minutes of an adequate airway with oxygenation of the patient, and the surgical ability to carry out a thoracotomy.

2. Evidence to date seemingly indicates that younger patients without previously damaged hearts have a greater expectation of long-term survival, necessitating extreme discretion in undertaking such extensive therapeutic measures.

Summary

The fourth presumed case of long-term survival following ventricular fibrillation complicating acute myocardial infarction is reported. The presence of an 11-year history of hemochromatosis, with its attendant

complications, provided many unique aspects of this case. A discussion of the pertinent aspects and case summary are included.

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Psychogenic Polydipsia Cured by Water Intoxication Following Vasopressin (Pitressin)

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A form of polyuria in which the urine does not taste sweet was recognized by Thomas Willis in 1674. Diabetes insipidus-spurius was separated as a distinct entity from diabetes mellitus-verus by Frank in 1794.[1] Today it is evident, however, that the term diabetes insipidus has been used to indicate various polyurias of different etiology.[2] Among these, the recognition of psychogenic polydipsia, described in 1905 by Ramond and Achard under the name of potomania, is of special importance, as this is a "polyuria" which may be radically cured.

While in true diabetes insipidus the polyuria is due to a defective secretion of antidiuretic hormone, in psychogenic polydipsia there is a disturbance in thirst control not caused by impairment of production or release of antidiuretic hormone.

In the present communication we describe a case of psychogenic polydipsia with unusual features, notably the sudden onset of polydipsia following a small dose of prednisone (Meticorten) and its cure by a short course of vasopressin (Pitressin).

Report of Case

A German-born housewife, aged 40, was admitted to the medical department on Dec. 24, 1956, with a tentative diagnosis of diabetes insipidus. In 1947, she had immigrated to Israel, settled on a collective farm, and a half year later married. Her entire family, with the exception of her mother, had been killed during the war in Europe. At the age of 11 she had mastoiditis followed by meningitis. Since then she has suffered from recurrent headaches without specific localization and not of the migraine type. Menstruation appeared at the age of 12, was never regular, and was accompanied usually by large blood loss. She had never become pregnant, and hysterosalpingography, performed in 1955, revealed obliteration of both tubes. Various types of treatment, including tubal insufflation, had been of no avail.

During the first year after arrival in Israel she lost 15 kg. and in the second year an additional 5 kg. She had worked strenuously but eaten little. Since 1950 she had suffered from attacks of low-back pain, lasting for a few days and frequently accompanied by swelling in the sacral region. Repeated examination, including radiography, did not disclose pathology of the spine. She was treated by infiltration of the sacral region with procaine hydrochloride (Novocaine) and hydrocortisone, with temporary good effect. The patient is known to be allergic to fish and to sulfonamide drugs, both of which cause edema of the face.

Two and a half months before admission she had been given prednisone for the increasingly severe back pains. During one single day the patient took three tablets of 5 mg. each. After the first tablet she experienced palpitation and dizziness, and a few hours after the third tablet she suddenly felt very thirsty and began to drink huge quantities of water. The patient was very positive about the sudden appearance of the thirst. Since then, until admission to our department, she had drunk 6-7 liters of water daily and produced a correspondingly large quantity of urine.

On admission she was thin and slightly pale and complained continuously of thirst and drank large quantities of fluids. Her fluid intake averaged 7 liters a day. The blood pressure was 110/70 mm. Hg. Except for tenderness on pressure over the sacrum, the physical examination was negative. There were no abnormal neurological findings, except for limitation of both visual fields on gross examination. The eyegrounds were normal. Perimetry showed bilateral tubular vision. The urine was normal; the daily urinary output amounted to 6-7 liters; the specific gravity ranged on repeated examination from 1.000-1.004. The blood urea nitrogen was 24 mg. per 100 ml.; repeated examination showed a serum chloride 100-

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From the Department of Medicine D, Beilinson Hospital.

102 mEq. per liter, serum sodium 136-148 mEq. per liter, serum potassium 4.1-4.2 mEq. per liter. The urea clearance was 85% of normal. A lumbar puncture revealed clear fluid under normal pressure with no elements and a negative Pandy test. An oral glucose-tolerance test gave a normal curve. The 24-hour excretion of 17-ketosteroids was 11.3 mg. and of 11-oxysteroids, 2.5 mg.; FSH, 30 mouse units; LH, 15 mouse units, all within the normal range in our laboratory. The basal metabolic rate was +11%. The electroencephalogram was normal. Radiography of the spine, skull, sella turcica, and foramina opticae revealed no abnormalities.

Careful observation of the patient showed that, in spite of her continuous thirst, her tongue was never dry. Also, when she slept well after taking a barbiturate, she did not pass urine during the night for a period of seven to eight hours.

A urine concentration test, done in spite of ardent objection by the patient, was normal: the specific gravity increased from 1.002 to 1.025 after 16-hour fluid deprivation. A Carter-Robbins test [4] was done to investigate the response of the osmoreceptors to hypertonic sodium chloride solution. The result of the test was normal; after the intravenous administration of hypertonic salt solution there was definite antidiuresis.

The diagnosis of psychogenic polydipsia was made in view of the normal urine concentration test, the normal response to the Carter-Robbins test, lack of evidence for other diseases causing polydipsia, and the tubular vision, a common finding in hysteria. The patient was examined by a psychiatrist, who found many hysterical traits. Orthopedic examination being negative, it was assumed that the back pain was also a hysterical manifestation.

Treatment.—Since the patient objected to psychiatric therapy, another treatment was tried. She was given vasopressin tannate oil, I. M., 2.5 units daily for five days. On the first day of treatment her urinary output decreased to 500 ml. and then remained stationary between 2-2.3 liters per day for the next four days. Her water intake during the same period, however, was 4-5 liters in addition to the fluid contained in the regular food. The continued excessive drinking in spite of the decrease in urinary output and in the absence of fever or sweating provided additional evidence of the psychogenic nature of her polydipsia. Her weight increased 3.5 kg.; she felt as if her body was swollen, and she complained of nausea and a heavy pressure in the head and chest—all signs of water intoxication. On the fifth day of vasopressin treatment the patient limited her water intake spontaneously to about 1,500 ml. per day. Subsequently, injections of isotonic saline were substituted for the vasopressin without recurrence of the polydipsia. After six more days the saline injections were discontinued and the water intake did not exceed 2 liters. The patient gradually felt better and was not thirsty any more but continued to complain of low-back pain. She was sent home on the 23d day of hospitalization, 8 days after the vasopressin treatment was stopped.

Two months later the patient was admitted for reexamination. She drank 1.6-2 liters of water per day; the urinary output was 1,400-2,500 ml. per day, the specific gravity reaching 1.010 and, after an 18-hour fluid fast, 1.026. There was still tubular vision. After four more months she was seen in the outpatient clinic, still complaining of severe low-back pain. She informed us that she drank not more than 2 liters a day and that the polyuria had disappeared. Neurologic examination was normal, except for tubular vision. At the request of the patient's family, she was referred to a psychiatrist but refused to go. Reexamination after one year showed the patient healthy, without complaints, with a normal urine output and specific gravity up to 1.025.

Comment

An essential requirement for the diagnosis of psychogenic polydipsia is the demonstration of a normal neurohormonal regulation of antidiuretic hormone secretion. The neurohormonal system involved in the secretion of the antidiuretic hormone consists of the hypothalamic supraoptic and paraventricular nuclei, the posterior pituitary, and the tracts connecting these structures. Demonstration of a normal function of this system requires the attainment of a high urinary specific gravity after limitation of fluid intake and an antidiuretic response to the intravenous administration of hypertonic salt solution (Carter-Robbins test [4]). The diagnosis of psychogenic polydipsia, however, may present considerable difficulties.

Organic lesions of the hypothalamus may cause primary polydipsia. Bellows and van Wagenen [5] and Witt et al.[6] produced in dogs primary polydipsia by injury to the hypothalamus. Andersson [7] observed polydipsia, preceding polyuria, in goats following injection of hypertonic salt solution into the hypothalamus in a region in the vicinity of the third ventricle. He concluded that nervous tissues involved in the thirst-regu-

lating mechanism can cause primary polydipsia without simultaneous inactivation of the supraopticohypophysial system. The subject of experimental hypothalamic polydipsia has been extensively reviewed by Strauss.[8] Julien-Marie (cited by Decourt[9]) reported a child with Schüller-Christian disease having polyuria and polydipsia but a normal urinary concentration test. Primary polydipsia due to a tumor in the hypothalamus was described by Fulton and Bailey[10] and due to inflammatory conditions by Kourilsky.[11] Cases of true diabetes insipidus, presenting initially as psychogenic polydipsia, have been reported by Fanconi.[2] This author described a young child who had developed polyuria and polydipsia but had a normal urinary concentration test. The diagnosis of psychogenic polydipsia was made, and the patient was treated for behavior disorder. Gradually, however, the picture changed into that of true neurohormonal diabetes insipidus. At the age of 24, there was no antidiuresis after intravenous hypertonic salt solution and no increase in the specific gravity of the urine during a concentration test; there was, however, a prompt response to antidiuretic hormone. In such cases, the early stage, termed pseudopsychogenic polydipsia, is considered the forerunner of true diabetes insipidus. Fanconi stresses the organic basis of this polydipsia, and it is pertinent that the father of this child suffered from true diabetes insipidus.

On the other hand, psychogenic polydipsia may simulate true diabetes insipidus. Decourt et al.[9] described a patient with polyuria and polydipsia in whom water restriction caused dehydration and fever and in whom no antidiuresis was induced by the infusion of hypertonic salt solution. Vasopressin administration reduced the polyuria, and the patient gained weight. When the vasopressin was replaced by a placebo and also after discontinuation of the placebo administration, the polyuria and polydipsia did not recur and the response to hypertonic salt solution and to water deprivation became normal. The initial abnormal response to stimuli of the antidiuretic hormone secretion mechanism was explained by reversible inhibition of the activity of the hypothalamic pituitary axis, caused by prolonged excessive water intake.

Excessive water drinking may be followed by a temporary inability to secrete antidiuretic hormone, i. e., reversible diabetes insipidus (Holmes and Montgomery,[12] Lhermite,[13] Tournay[14]). Whether prolonged excessive fluid intake may cause permanent diabetes insipidus is not clear. Suggestive is the case of a physician, mentioned by Lhermite,[13] who drank voluntarily large quantities of water in order to prevent vascular and kidney disease and who after a few months, when trying to limit his fluid intake, was unable to do so and finally died in cachexia.

All these observations—true diabetes insipidus masquerading as psychogenic polydipsia; psychogenic polydipsia simulating diabetes insipidus, and the transformation of psychogenic polydipsia into diabetes insipidus, reversible or possibly even irreversible—illustrate the difficulty of differentiating between these two conditions.

Additional tests may be of value. Nicotine is known to stimulate antidiuretic hormone excretion by action upon the hypothalamus.[15] In true diabetes insipidus there is no antidiuretic response to nicotine.[15,16] Dingman et al.[17] found a diminished response to nicotine in the presence of a normal response to water deprivation and to hypertonic saline in three patients with psychogenic polydipsia, in one of them developing consequent to cortisone therapy and disappearing after the drug was discontinued. In this patient, however, the nicotine test remained abnormal in spite of the disappearance of the polydipsia and the polyuria. The polydipsia and the lack of response to nicotine were explained by the assumption of a disturbance in a hypothalamic thirst center, adjacent to the supraoptic nuclei. It is evident, however, that if the action of nicotine is on a hypothalamic thirst center,

lack of response to nicotine can not differentiate between thirst due to an organic lesion or psychogenically induced. Unfortunately in our patient the nicotine test was not performed.

According to Holmes and Montgomery,[12] measurement of salivary flow after vasopressin administration may serve to differentiate between true diabetes insipidus and psychogenic polydipsia, the flow of saliva increasing in the former but remaining unchanged or decreasing in the latter. Salivary flow in our patient after five days of vasopressin administration, when the polyuria had subsided, apparently did not increase, as far as could be gathered from the patient's unchanged complaint of dryness in the mouth.

As observed in the case described by Decourt et al.[9] and in ours, vasopressin administration, inducing the extremely unpleasant state of water intoxication due to persistence in drinking, seems to be a reliable test for the diagnosis of psychogenic polydipsia. Additional evidence for the psychogenic origin of the polydipsia will be provided by the persistence of the antidiuretic effect when the vasopressin is replaced by a placebo and even when the placebo administration is discontinued.

Vasopressin administration followed by a placebo evidently is also an effective treatment for psychogenic drinking, as demonstrated both by Decourt's [9] patient and ours, the latter not relapsing during a follow-up period of almost two years. Effective treatment of this condition by sleep therapy has been reported by Baumann.[1]

As to a possible etiologic role of the prednisone taken by our patient shortly before the appearance of the polydipsia, adrenal steroids were shown to produce polyuria, presumably by inhibiting a hypothalamic mechanism for antidiuretic hormone release not regulated by extracellular tonicity.[18] Cortisone diminishes the antidiuretic response to nicotine probably by the same mechanism.[19,20] Hypothalamic lesions in the region of the supraoptic nuclei have been observed in animals receiving large doses of cortisone.[21] In a case of psychogenic polydipsia described by Dingman et al.[17] the polydipsia appeared after treatment with cortisone, 200 mg. daily, for a three-week period. The mechanism by which prednisone in a dose as small as 15 mg. may have caused the polydipsia in our patient is difficult to understand.

Summary

A patient with psychogenic polydipsia was successfully treated by a short course of vasopressin (Pitressin) which induced water intoxication.

Vasopressin administration is considered a reliable test as well as an effective treatment for psychogenic polydipsia.

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Aortoiliac Occlusion (Leriche Syndrome) Resulting from Past Trauma

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The syndrome of chronic occlusion of the aorta and iliac arteries, as described by Leriche in 1940, has been attributed to atherosclerosis by practically all who have written on this condition.[1-3] However, the histories of the patients to be described lead one to believe that the atherosclerosis and thrombosis in some patients may be secondary to past trauma to the abdominal aorta rather than the primary cause of the syndrome. A patient who drew our attention to the fact that the abdominal aorta is susceptible to injury was a 36-year-old man, seen in 1954, who was struck in the abdomen by a wooden beam moving at high speed. At operation the abdominal aorta was found to be thrombosed. This is an extreme example of trauma resulting in acute thrombosis of the abdominal aorta. It occurred to us that trauma of less degree may subsequently result in occlusion of the abdominal aorta. This idea receives support from the experimental work of Gillman and Hathorn,[4] who showed that a single acute but severe injury to arteries in rats may be followed, months later, by sclerosis. Five patients have been seen with histories of severe trauma who subsequently developed aortoiliac disease. Three of these patients gave histories of severe automobile accidents at the ages of 9, 13, and 18 years, with development of symptoms of chronic aortoiliac occlusion at the ages of 24, 45, and 37 years, respectively. The first two patients had been run over across the abdomen. Two other patients were seen with this syndrome in whom the history of trauma, other than by automobile, was such as to lead one to suspect a relationship.

A relationship between atherosclerotic occlusion of the aorta and iliac arteries and an injury that has occurred many years previously can readily be obscured by the insidious development of atherosclerosis in humans, with failure to manifest itself until the appearance of symptoms of ischemia. Duguid and Robertson[5] and Gillman and Hathorn[4] have pointed out the importance of trauma to rapidly growing arteries in childhood in the later development of atherosclerosis at the injured sites. Injuries to the aorta occurring under the age of 21 may be of particular importance, since this artery must grow rapidly in length during this period as the child or youth grows in height.[5] Overloading of the intima with fibrous tissue may predispose this site to later atherosclerosis.

That severe nonpenetrating trauma may result in injury to the aorta has been well recognized. For example, Steinberg[6] has reported five patients with aneurysms first diagnosed years after automobile injuries to the chest.

It has been somewhat of a mystery as to why so many of the patients with aortoiliac occlusion are relatively young men, between the ages of 30 and 50, with atherosclerosis and thrombosis of an artery as large as the abdominal aorta, a vessel measuring 1.7 to 2.0 cm. in diameter. Trauma could explain a localized type of atherosclerotic occlusion such as this, at least in some of these patients. The abdominal aorta is susceptible to severe trauma, lying as it does between the ribs and iliac crests anterior to the vertebrae.

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Report of Cases

CASE 1.—A 44-year-old man was first seen in March, 1955, complaining of pain and tingling in the right foot which had started three weeks previously. He also gave a history of a cramp in the right hip and calf, on walking two blocks, present since the age of 24. He gave a history of impotence for several years. His past medical history included the pertinent fact that he was run over by an automobile, at the age of 9 years, across the lower abdomen. He stated that he was bruised but was patched up at a hospital and sent home the same day. He required a left inguinal herniorrhaphy, at the age of 10 years, which he believed was necessitated by the accident. No symptoms were present in the legs until the age of 24. He smoked 30 cigarettes a day and had no history of diabetes mellitus. The examination disclosed the typical findings of occlusion at the bifurcation of the aorta. There were no pulses palpable in either leg, even in the abdomen over the aorta. Both feet blanched rapidly on elevation and flushed slowly on dependency. The right foot was ruborous on dependency. Blood pressure was 140/90. An aortogram disclosed occlusion of the abdominal aorta below the level of the origin of the renal arteries (Fig. 1). In July, 1955, a severely atherosclerotic occluded aorta was resected and a graft inserted. The graft extended from just below the renal arteries to the right external iliac and left common femoral arteries. The patient did well following the graft but died suddenly in August, 1956. The cause of death was unknown. There was no autopsy.

Fig. 1.—Aortogram of patient, 44 years old, run over by an automobile across the abdomen at the age of 9 years. Abdominal aorta occluded just below renal arteries.

Fig. 2.—Severe calcification at bifurcation of abdominal aorta in patient 52 years old, who was run over by an automobile across the abdomen at the age of 13.

CASE 2.—A 52-year-old man was seen in May, 1957, with a history of intermittent claudication at one block, starting at the age of 45. At the age of 13, he was run over across the abdomen by an automobile. He stated that the tires just missed his hips and chest. He was hospitalized for only three days. He had no further complaints until he developed the leg symptoms, 32 years later. Examination disclosed a faint left femoral pulse with a bruit heard over the abdominal aorta and also over the right femoral artery, which was palpable. His oscillometric readings were greatly reduced in the left leg and moderately reduced in the right. X-ray showed extensive calcification of the abdominal aorta, including the bifurcation and iliac arteries (Fig. 2).

CASE 3.—A 37-year-old physician was first seen in September, 1945, with a history of intermittent claudication for the past nine months. He gave a history that he was in an automobile smash-up at the age of 18. He was bruised all over and had a fractured left patella. He was hospitalized for one day only. He had no complaints until 19 years later, when he developed pain in the legs on walking. Examination disclosed no right femoral pulse and a weak left femoral pulse. Oscillometric readings were almost zero in the right thigh and reduced in the left. In December, 1956, neither femoral pulse was palpable. The patient had a cholecystectomy in October, 1956. Examination of the abdominal aorta at this operation disclosed calcification and complete segmental occlusion of the lower portion at the bifurcation.

The following patients illustrate the susceptibility of the abdominal aorta and iliac arteries to severe trauma other than automobile accidents.

Case 4.—A white man, 52 years of age, gave a history of pain in the calves on walking less than two blocks, starting seven years previously, at the age of 45. He dated his difficulty in walking to a severe fall while hunting, with development of typical claudication in the legs two or three days later.

Examination disclosed no pulse at either femoral. Oscillometric readings were almost zero in both legs.

This patient was seen in 1948, before the days of vascular grafts. A bilateral lumbar sympathectomy was done, at which time the lower part of the abdominal aorta was found to be a fibrotic cord.

Although this patient did not recall whether there was injury to the abdomen, he did know that the fall was severe and that the difficulty in walking started several days later.

Case 5.—A 52-year-old man gave a history of inability to walk more than two blocks, of two months' duration. He complained of heaviness, particularly of the left leg up to the hip. His history of trauma was as follows. At the age of 23, he fell out of a second-story window flat on his feet. He stated that he had no injury. At the age of 25, he fell down a chimney 4 ft. wide, undergoing a 42 ft. fall during which his right leg was broken. At the age of 27, a steel cable came down and hit him on the back and flattened him. At the age of 28, he was on a boom that fell 20 ft., the support having given way, and he landed on his buttocks. The examination disclosed a faint left femoral pulse with no pulses below this. There was a bruit over the left femoral artery. Oscillometric readings were almost zero in the left leg. The left foot was colder than the right. X-ray disclosed calcification of the abdominal aorta. The hip claudication and the bruit suggested that the reduction in lumen was probably in the left iliac artery.

Even though the relationship between the trauma and the arterial occlusive disease in this patient is not clear-cut, he is included in this report to illustrate the almost complete lack of consideration of trauma as a factor in the subsequent development of atherosclerotic occlusion.

Comment

The abdominal aorta is susceptible to severe trauma, since it lacks the protection of the ribs and pelvis. It lies directly on the anterior surface of the lumbar vertebrae, the bifurcation being usually at the fourth lumbar vertebra, which is about the level of the upper part of the iliac crest and 2.5 cm. below the umbilicus, just to the left of it (Fig. 3). In thin persons, with the intestines empty, the pulsation of the abdominal aorta may be readily palpated.

Fig. 3.—Normal aortogram, showing the anatomic susceptibility of the abdominal aorta and its bifurcation to physical trauma between the ribs and the iliac crests.

In patients in whom the trauma has not been severe enough to thrombose the abdominal aorta the injury to this large artery, particularly in rapidly growing children, may set up a fibrotic site for later atherosclerosis. As Gillman and Hathorn [4] point out, at least some forms of arterial sclerosis may represent the end-result of a single, acute injury inflicted months or perhaps years prior to recognition of the terminal picture. Our cases suggest that local vascular injury producing intimal damage may not be clinically recognized and yet may be the initiating factor for the syndrome which we, in its final stages, know as aortoiliac occlusive disease (Leriche syndrome).

There was only one reference in the literature to trauma as a cause of thrombosis of the abdominal aorta, one case without a description of the case or type of trauma.[7] The discrepancy between the great number of severe traumatic injuries and the lack of reports of chronic aortoiliac damage may be due to the long interval in humans between the occurrence of the accident and the appearance of ischemic symptoms.

Boyd et al.[8] have reported a number of men under the age of 35 with what they called primary popliteal artery thrombosis with evidence that suggested local injury as the cause of the thrombosis. They believe that normal knee movement or minor sprains and strains may cause damage to the intima and thrombosis of the vessel. In the patients with aortoiliac occlusion reported here there was known severe trauma.

That atherosclerosis alone may not be the primary cause of thrombosis of the abdominal aorta in all cases is further suggested by the fact that patients with diabetes mellitus rarely develop thrombosis of the abdominal aorta, and yet atherosclerosis is a common complication of diabetes mellitus. At least 50% of arterial occlusion in the legs occurs in diabetics. Only 1 of 47 patients with aortic thrombosis, reported by deWolfe and his co-authors,[2] had diabetes mellitus. None of the patients reported here had diabetes mellitus.

Few patients with thrombosis of the abdominal aorta have heart disease which might be a source for embolism. Only 4 of the 47 patients reported by deWolfe et al.[2] had any evidence of myocardial ischemia. None of the patients reported here had evidence of heart disease.

Once an artery is scarred it possesses a lower threshold for development of atherosclerosis. Duguid and Robertson[5] have suggested that fibrotic healing of the aorta results in local impairment of the elasticity or flexibility of the intima, which leads to mechanical factors favoring thrombosis and deposition of lipids. Gillman and Hathorn[4] also comment on the intramural localization of lipid deposits in areas of previous vascular injury. It would appear that in some patients with the Leriche syndrome we may be dealing with moderatly severe injuries to the aorta that did not result in rupture or aneurysm but damaged the abdominal aorta sufficiently to produce a site for development of subsequent atherosclerotic occlusion with or without thrombosis.

Summary

Five patients are reported who developed aortoiliac occlusion years after automobile or other injuries. Two were run over across the abdomen in childhood, and one was in an automobile smash-up at the age of 18. Two other patients with other types of severe trauma with this syndrome are included in this report. The patients reported here lend clinical support to the experimental evidence that a single severe localized injury to an artery may result in subsequent arterial sclerosis. Too little emphasis has been given to trauma as a possible initiating factor that may result in the terminal picture of arterial occlusive disease, in our cases particularly aortoiliac occlusion or the Leriche syndrome. We do not imply that trauma initiates this syndrome in all cases, but it certainly seems significant in the cases reported.

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Pseudoinfarction Pattern Associated with Electrolyte Disturbance

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Introduction

The electrocardiographic changes associated with hyperkalemia have been well documented by previous writers.[1-4] These changes include (1) peaking of the T-waves; (2) increased depth of the S-wave, with lowering of the R-wave; (3) widening and then loss of P-waves; (4) ST-segment elevation associated with intraventricular conduction disturbances, resulting in a widened QRS complex; (5) prolongation of P-R interval, and (6) ventricular arrhythmias. Myers[5] has described an ECG pattern simulating myocardial infarction associated with hyperkalemia. Recently Levine et al.[6] likewise have described the electrocardiographic changes of acute myocardial infarction associated with hyperkalemia. In recent months we have had two cases similar in several respects to those of Levine in that they showed transient electrocardiographic patterns consistent with myocardial infarction. One of these ECG's has a pattern more suggestive of an "old" rather than recent infarction, and the second ECG presented an atypical pattern. At autopsy the first patient failed to show evidence of recent or old myocardial infarction. The tracing in the second patient, after return of serum potassium to normal levels, no longer showed the atypical pattern of infarction.

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Report of Cases

CASE 1.—This patient, a 32-year-old Negro man, was admitted to this hospital on June 15, 1957, in a semistuporous state. He had been a known chronic alcoholic. At the time of his admission he complained of vague low back pain associated with nausea and vomiting. These symptoms were accompanied by chills, fever, and a dark-colored urine. He apparently had been drinking heavily prior to admission, and delirium tremens appeared imminent. He denied any contact with known chemical toxins.

The patient was tremulous. The pulse rate was 100 per minute; the blood pressure, 110/80 mm. Hg, and the temperature, 100 F. Subconjunctival hemorrhages were noted, but there was no scleral icterus. A Grade 2 apical systolic murmur was present. The lungs appeared to be normal. The examination of the abdomen was negative.

On catherization, 150 cc. of urine was obtained. Urinalysis showed a 4+ reaction for albumin; glucose and bilirubin were not demonstrated. There was much cellular debris, with occasional granular casts and white blood cells, but no red blood cells were found.

Laboratory Findings in Case 1

	6/17	6/19	6/20	6/24	6/26	6/27	6/28	7/1	7/2	7/3	7/4
Na, mEq/liter	138		144	148	137	136	132	144		130	
K, mEq/liter	4.5	5.4	6.9	8.7	9.0	9.7	8.2	6.9	6.5	5.8	
Cl, mEq/liter	91		92	90	85	82	81	102		101	
CO_2, mEq/liter	139	19.3	30.6	12.9	11.9	10.0	7.5	6.8	7.8		
NPN, mg. %	152	160	190	194		347	400	340	256	160	234
Creat., mg. %	80	10.6	11.4	16		15.6	15.2	11.8	10.8		10
Cal, mg. %					7.7						

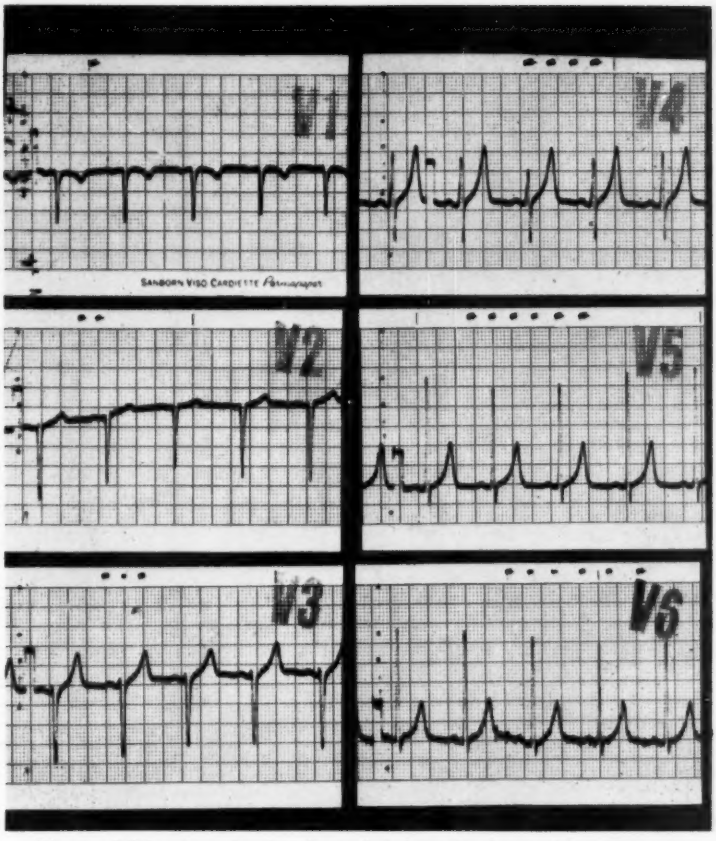


Fig. 1.—ECG taken shortly after admission, showing peaking T-waves.

Three days later, when the patient was considerably less obtunded, several new facts were brought to light. In addition to drinking very heavily prior to admission, the patient had worked in a closed room with a cleaning agent which contained 56.8% paraffin, 30.6% naphthane, and 12.6% aromatic spirits.

For a period of 60 hours, from June 17 till June 20, 1957, the patient was completely anuric. At this time the patient had a serum potassium level (Table) of 6.9 mEq. per liter, and the T-waves in the left precordial leads showed some peaking (Fig. 1).

On June 21, the patient developed a pericardial friction rub. He put out 470 cc. of dark urine, which had a 4+ reaction for albumin and contained oval fat bodies and blood casts. The ECG pattern (Fig. 2) showed similar T-wave changes. On June 24, 1957, the serum potassium level had risen to 7.7 mEq. per liter and the ECG (Fig. 3) showed tall peaked T-waves in V_2 and V_4 and somewhat lower but peaked T-waves in standard Leads I and II. When the serum potassium had reached a level of 9.0 mEq. per liter, on June 26, the ECG (Fig. 4) showed high peaked T-waves in almost all leads. In addition there was a first degree atrioventricular block.

On June 27, 1957, the nonprotein nitrogen was 347 mg. % and the potassium level was 9.7 mEq. per liter. Clinically the patient appeared to be deteriorating, even though his urinary output was over 500 cc. per day. His ECG (Fig. 5) showed a pattern similar to that in the past, but in addition a Q-wave was noted in aV_L. The following day, there was a classical pattern of anteroseptal myocardial infarction (Fig. 6). At this time the serum potassium level was 8.2 mEq. per liter.

By July 1, 1957, the patient showed clinical improvement. His serum potassium level had fallen to 6.9 mEq. per liter, and, though the ECG

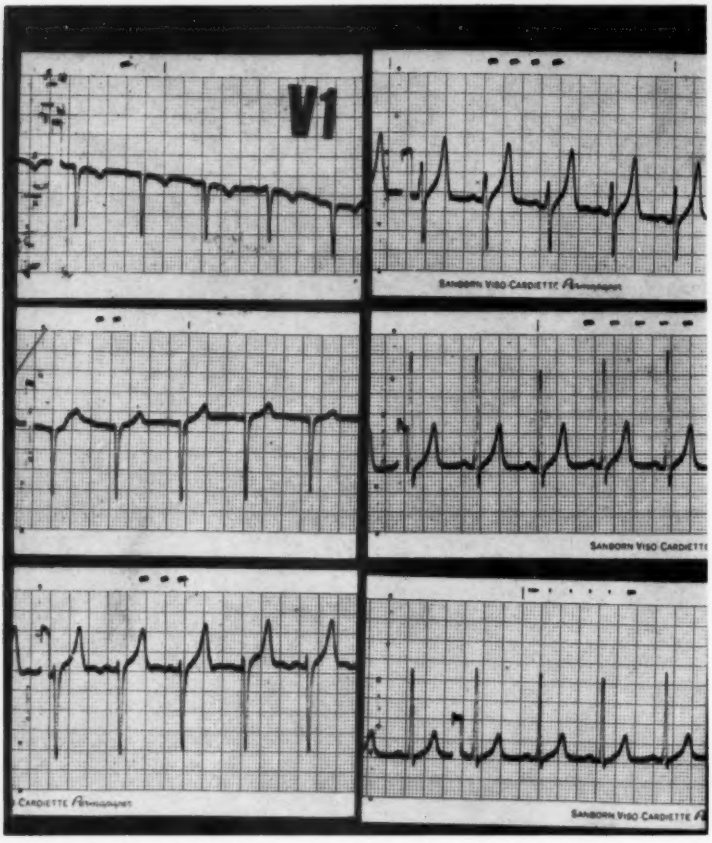


Fig. 2.—ECG (June 21, 1957) showing similar changes.

(Fig. 7) showed sinus tachycardia, there was little to suggest hyperkalemia; the pattern suggestive of mycardial infarction was no longer present.

Subsequent ECG's, taken on July 2 and July 3, 1957 (Fig. 8), showed diminished R-waves in V_2 and V_3. On July 3, the patient developed pulmonary rales, hematemesis, melana, and peripheral collapse. The patient died the following morning. Postmortem examination failed to show any evidence of old or recent myocardial or pulmonary infarction.

Case 2.—This 64-year-old Negro male machine operator was admitted to this hospital on March 7, 1957, because of pain in the left costovertebral area of six week's duration. Though the patient had hesitancy, frequency, nocturia, and urinary dribbling for years, he recently noted an increase in these symptoms. In the two weeks prior to admission, he was anorexic, with nausea and vomiting for about three days. With the latter complaints he also experienced singultus.

On physical examination the patient appeared chronically ill and dehydrated. The heart was slightly enlarged, but the lungs were clear. Blood pressure was 170/84 mm. Hg; pulse, 80 beats per minute, and temperature, 97.6 F. There was some left costovertebral angle tenderness. The prostate was markedly enlarged, with a firm fixed nodule in the right superior pole.

On the morning after admission chemical analysis of the serum revealed the following values: nonprotein nitrogen 152 mg. %, creatinine 14.7 mg. %, Co_2 8.3 mEq. per liter, chloride 108 mEq. per liter, calcium 11.0 mg. %, sodium 136 mEq. per liter, and potassium 9.5 mEq. per liter. Urinalysis showed 2+ albumin, and the microscopic examination showed 1 granular cast and 2-3 clumps of white blood cells per high-power field. An ECG on March 9, 1957, was interpreted

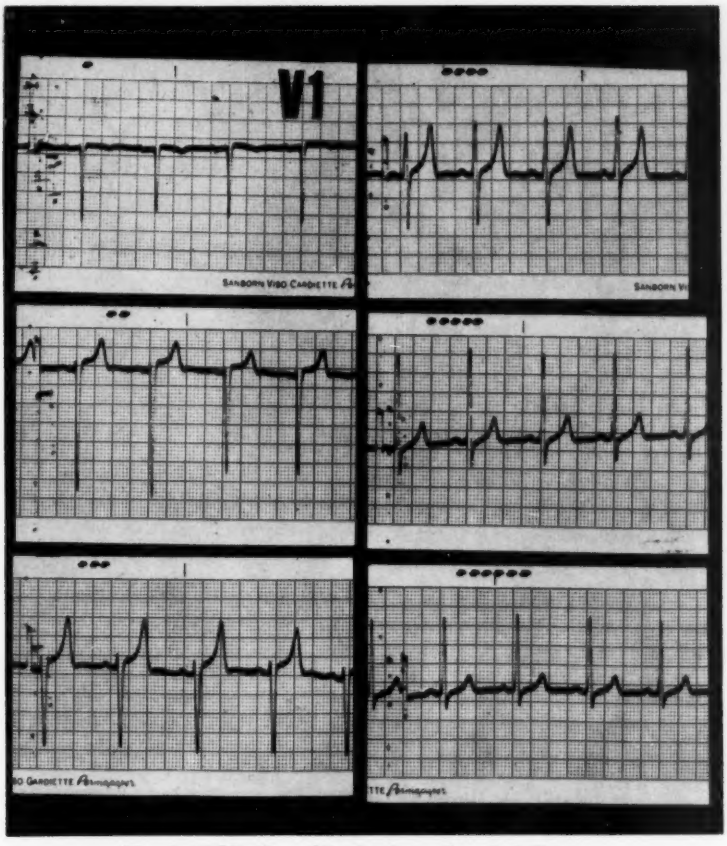


Fig. 3.—ECG (June 24) showing tall peaked T-waves.

as an atypical pattern suggestive of anteroseptal infarction with intraventricular conduction defect (Fig. 9). Peaked T-waves were present in standard Leads II and III and aV_F. A very small Q-wave was noted in V_1 and a broad Q-wave in V_5-V_6. The T-waves were diphasic in all the precordial leads.

The patient was thought to be dehydrated and to have pyelonephritis, renal and postrenal azotemia, and hyperkalemia. The postrenal azotemia was thought to be due to prostatic hypertrophy and a possible carcinoma of the prostate. Within two days (March 11) the patient was rehydrated, but the azotemia and hyperkalemia persisted though to slightly less degree (creatinine 11.4 mg. % and serum potassium 8.6 mEq. per liter). At this time an ECG (Fig. 10) showed nonspecific ST-segment changes; the T-waves were no longer peaked, and the abnormal Q-waves were no longer present. The previously mentioned conduction defect had disappeared.

On March 18, 1957, a retrograde pyelogram showed moderately severe blunting and dilatation of the left minor calyces, consistent with hydronephrosis and pyelonephritis. The ureteralvesicular orifices were cystoscopically observed to be partially occluded by a huge prostate. A biopsy of the prostate confirmed the impression of carcinoma. By March 28, the level of nonprotein nitrogen had fallen to 68 mg. % and creatinine to 1.9 mg. %, accompanied by marked clinical improvement in the patient. On April 6, 1957, the serum level of nonprotein nitrogen was 43 mg. %; CO_2, 23.7 mEq. per liter; sodium, 142 mEq. per liter; chlorides, 102 mEq. per liter, and potassium, 4.9 mEq. per liter. The ECG failed to show any of the previous abnormalities (Fig. 11).

It is of interest that the electrocardiographic pattern preceded by several days the restoration to normal of the serum level of potassium.

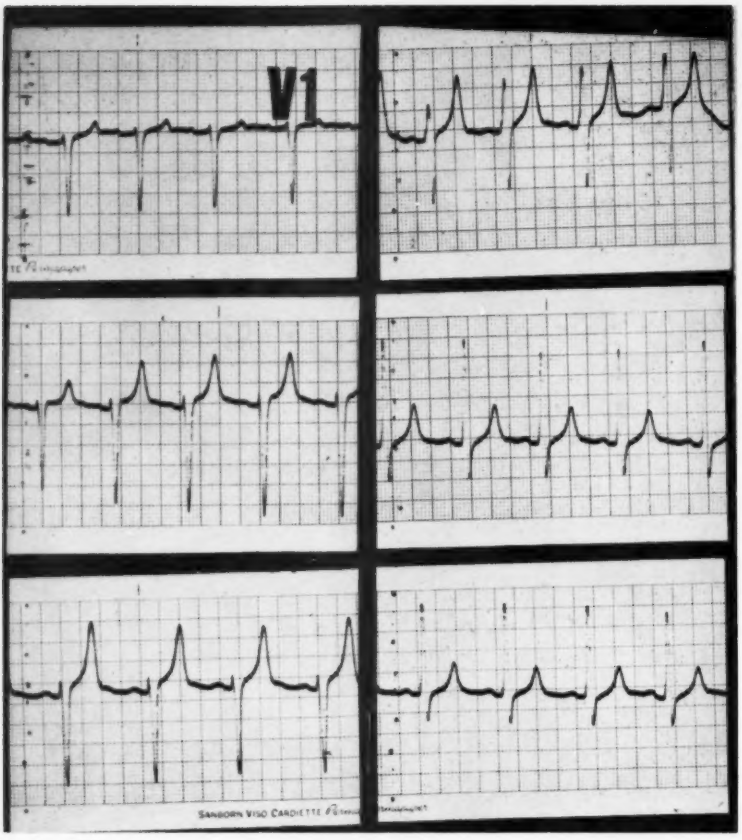


Fig. 4.—High peaked T-waves in almost all leads in addition to first-degree AV block.

Comment

Various ECG patterns have been misinterpreted as myocardial infarction. Only recently have electrolyte disturbances been added to this general category. In our two cases several points deserve emphasis. Our first patient abruptly developed the pattern of an "old" myocardial infarction in a period of 24 hours. The characteristic pattern of an evolving myocardial infarction was never seen in this patient. This is different from the patients reported by Levine et al.,[7] in whom the pattern of acute damage was demonstrated. It is of interest that the ECG changes were most prominent when the serum potassium was not at its highest level. On both June 26 and June 27, 1957, the serum potassium level was higher than on June 28, when the pronounced infarction pattern was noted. It has been stated that the acidosis per se can give a pattern suggestive of hyperkalemia [8] and hyponatremia and hypocalcemia can aggravate hyperkalemia.[9] Hypermagnesemia is also known to cause electrolyte changes similar to those of hyperkalemia.[10] Elevated serum sodium and calcium may neutralize the effects of an elevated serum potassium.[11] Probably this was the case to some extent on June 24, 26, and 27, 1957, when the serum sodium and CO_2 were at higher though not normal levels. In this regard the ECG was probably of more

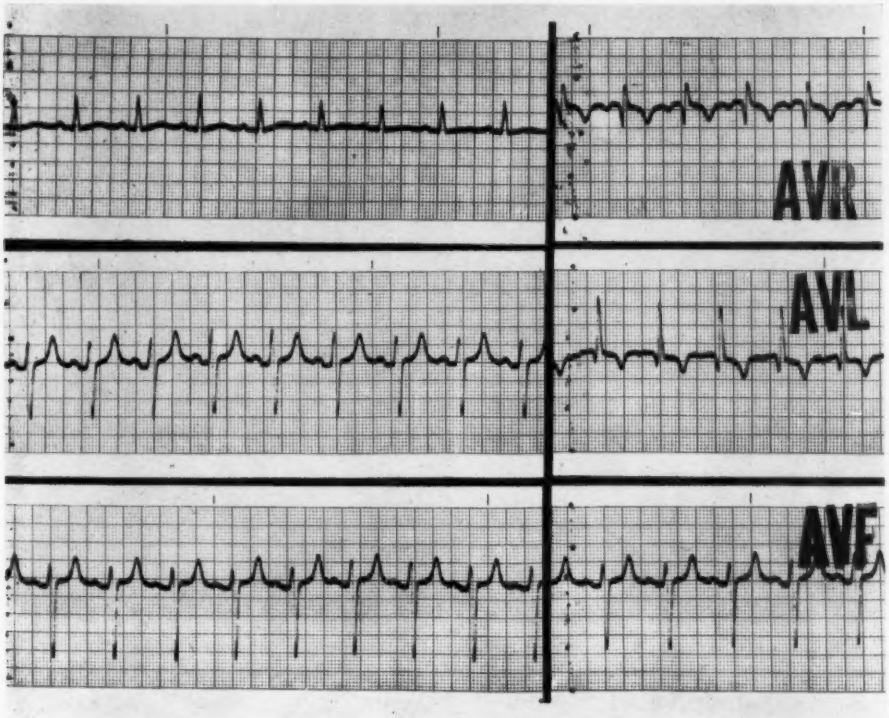
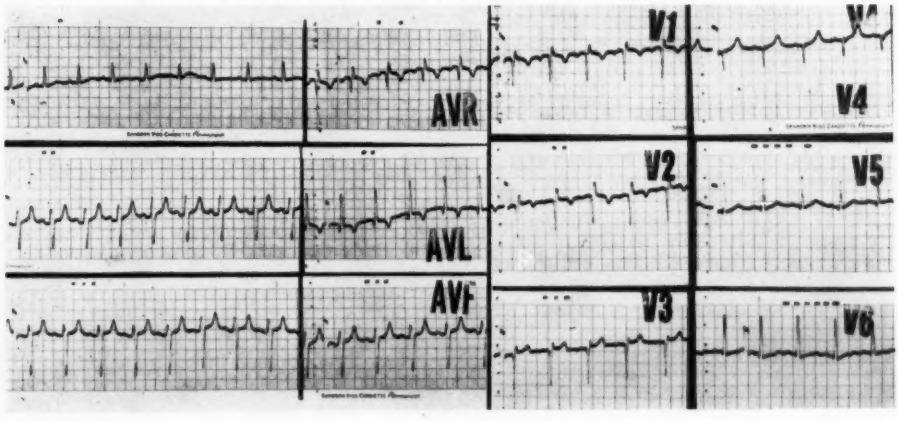


Fig. 5.—Q-waves now present in aV_L.

Fig. 6.—ECG shows classical pattern of anteroseptal myocardial infarction.



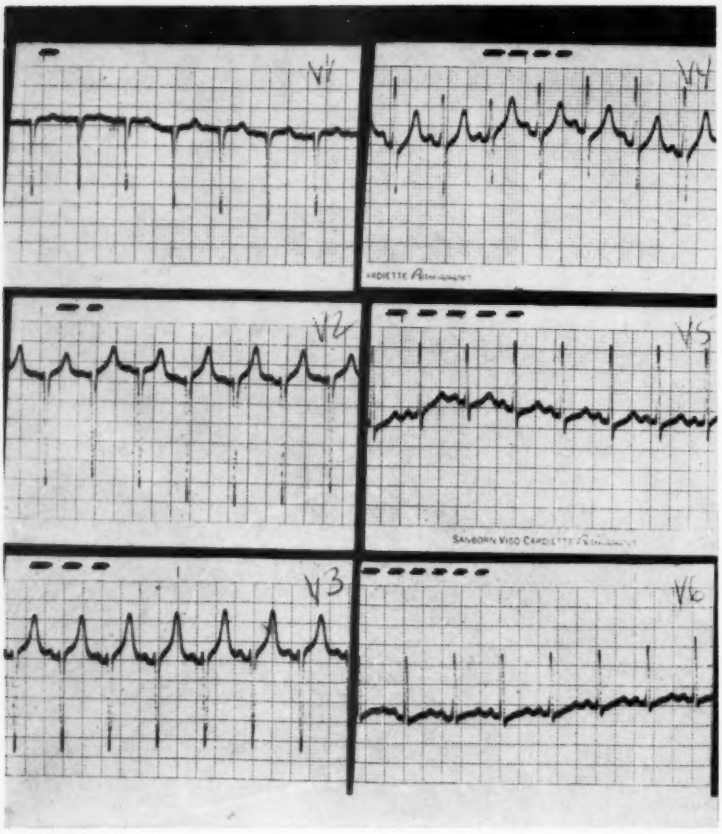


Fig. 7.—ECG shows sinus tachycardia but none of the previously mentioned abnormalities.

help than the chemical tests, for on June 28 the serum potassium had fallen and the patient appeared to be going into the diuretic phase and hypokalemia might have been in the offing. Further concern for such an impending problem was considered in view of the acidosis, for under such circumstances the serum level of potassium does not accurately reflect total body potassium.[12,13]

In the second case the infarct pattern is not at all typical but does demonstrate Q-waves in the right precordial leads. The elevated ST segments, well demonstrated in V_1 and V_2, appear very similar to the patterns demonstrated in Levine's paper. The serial graphs did not demonstrate an infarction pattern or the usual evolution that would be seen in pericarditis. In neither case was there evidence of left or right heart failure when the infarct pattern was most pronounced.

Summary and Conclusion

Two patients with hyperkalemia who had the ECG pattern of myocardial infarction are presented. In both cases the electrocardiographic evidence of infarction disappeared with the decrease in the serum potassium. Though we are not able to prove definitely that the second patient did not have infarction, it seems very improbable in view of the subsequent ECG's. However,

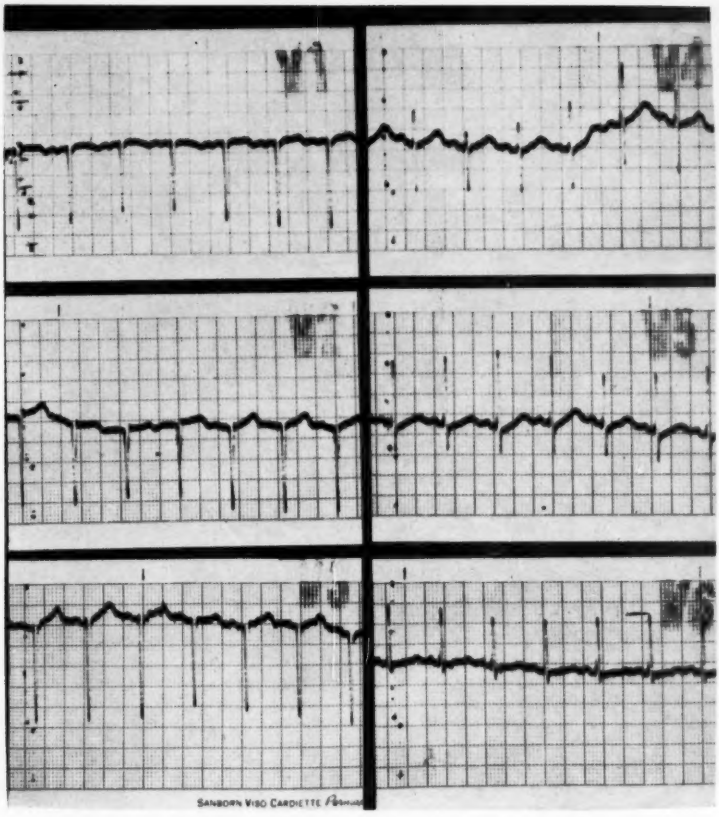


Fig. 8.—ECG (July 3, 1957) shows diminished R-waves in V_3 and V_5.

in the first patient, pathologically there was no evidence of myocardial or pulmonary infarction.

Though it is readily apparent that there is a definite relationship between hyperkalemia and the previously described ECG patterns, many other factors may be instrumental in contributing to these abnormalities. This is suggested by the fact that the highest level of serum potassium did not coincide with the ECG pattern of infarction. Other electrolytes, such as sodium, magnesium, and calcium, and the degree of acidosis are known to influence the relationship of serum potassium and the physiologic state of cardiac muscle. While Levine's patients had the electrocardiographic pattern suggestive of acute infarction, one of our patients presented the electrocardiographic pattern of an "old" infarct which developed abruptly. In both cases, the abnormality of electrocardiogram disappeared within two days.

Drs. Hyman J. Zimmerman and Paul Heller gave advice and reviewed the manuscript.

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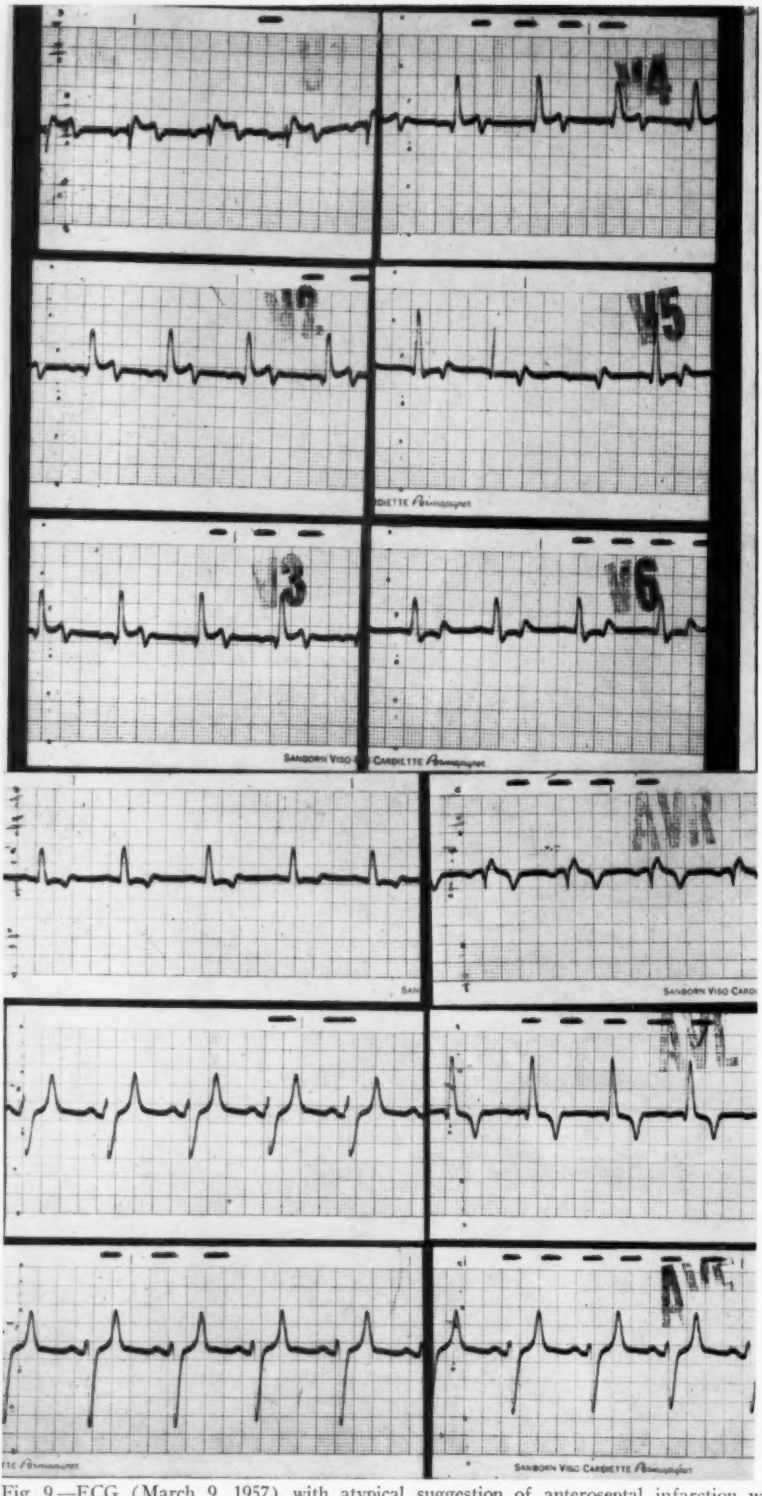


Fig. 9.—ECG (March 9, 1957) with atypical suggestion of anteroseptal infarction with intraventricular defect.

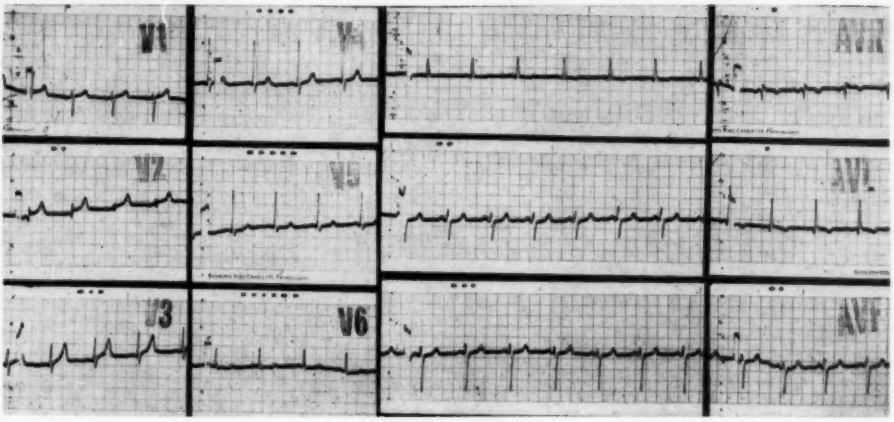
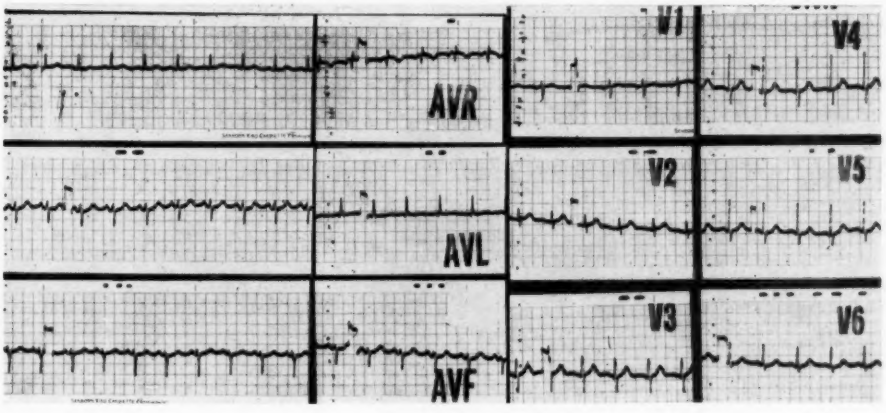


Fig. 10.—ECG shows nonspecific ST segment changes in T-wave, and Q-wave abnormalities no longer present.

Fig. 11.—ECG at this time fails to show any of the previous abnormalities.



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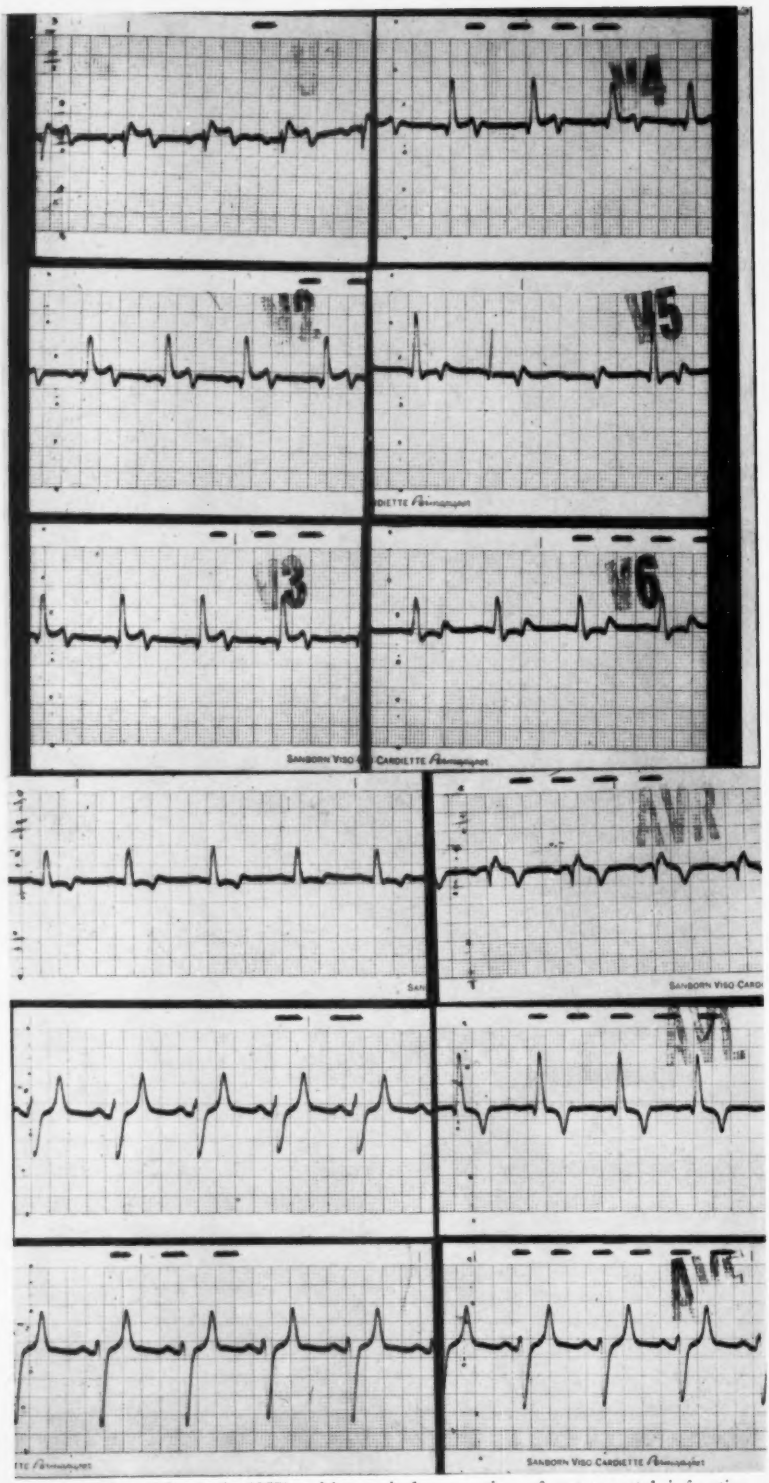
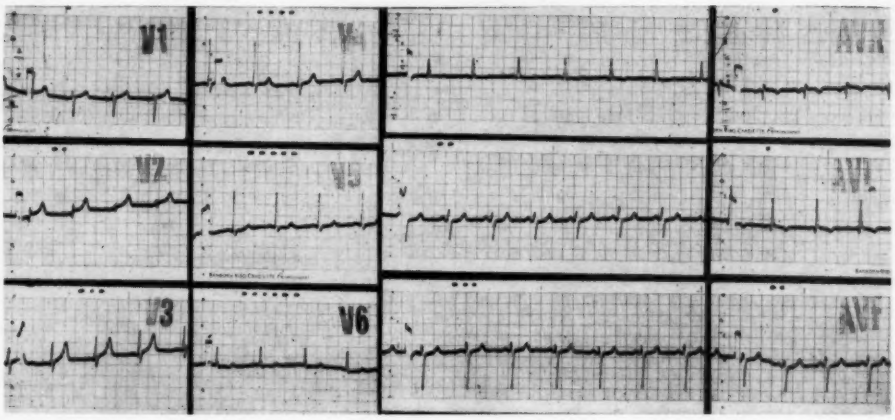


Fig. 9.—ECG (March 9, 1957) with atypical suggestion of anteroseptal infarction with intraventricular defect.



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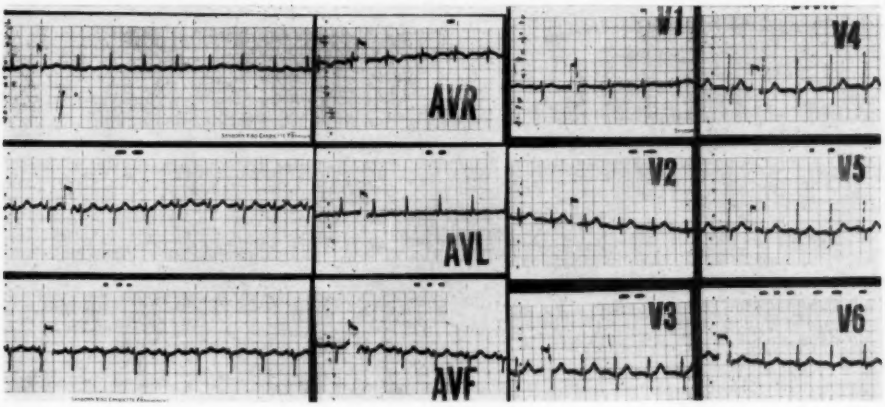

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Idiopathic Hemochromatosis in a Thirty-Nine-Year-Old Woman

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The commonly accepted concept of idiopathic hemochromatosis is that it is primarily a defect of the intestinal mucosal barrier to excess iron absorption. This results in slowly increasing body stores of this element, eventually leading to fibrosis in the liver, pancreas, heart, and other organs. The well-known decreased incidence of this condition in females has been attributed to the protective effect of menstrual bleeding and iron loss in pregnancy and lactation. Finch and Finch reviewed the existing literature of this disease in 1955, summarizing the findings in 787 patients. They noted its occurrence in only eight women less than 40 years of age and mentioned that in approximately 50% of affected women a history of decreased or absent menstrual flow was recorded.

In view of these facts, a case of hemochromatosis occurring in a 39-year-old woman with a history of menorrhagia is considered of sufficient interest to justify reporting.

Report of Case

The patient was a 39-year-old housewife when she was seen for the first time, on Sept. 27, 1956. At that time she complained of morning nausea of four weeks' duration. There was also moderate fatigue and occasional mild diarrhea but no other significant gastrointestinal complaints. System review was essentially negative. Past history included a urinary infection in 1953, at which time her physician had noted malar telangiectasia and had performed an L. E. test, which was negative. There had been no pregnancies. Her menstrual history was of considerable interest. The menarche had occurred at the age of 13, and her periods were at 28-day intervals, lasting 3 to 4 days. A dilatation and curettage was performed in 1943 and again in 1955 for menorrhagia. Following the second procedure she had only minimal bleeding every 60 to 90 days. There was no history of unusual iron or alcohol ingestion. Family history was not contributory, there being 13 siblings living and presumably well.

Physical Examination.—The patient appeared well developed and well nourished. There was striking gray-brown pigmentation of the exposed skin of the arms, face, and neck. Numerous dilated capillaries were noted in the malar regions, and a few spider angiomata were present on the anterior chest. There was moderate palmar erythema. The blood pressure was 170/94. A firm, nontender liver edge was palpable 6 cm. below the right costal margin. The spleen could not be felt. The remainder of the physical examination was essentially negative.

Laboratory Findings.—The hemoglobin was 14.5 gm., with a normal white blood cell count and differential. Total serum bilirubin was 0.3 mg. %. The cephalin-cholesterol flocculation was a trace at 48 hours, with a thymol turbidity of 6.0 units. The total protein was 6.5 gm/100 ml., albumin being 3.8 gm/100 ml. and globulin 2.7 gm/100 ml. Sulfobromophthalein (Bromsulfalein) retention at 45 minutes was 7%. An oral glucose-tolerance test with 100 gm. of glucose revealed the following results: fasting 88 mg. %, 30 minutes 200 mg. %, one hour 175 mg. %, two hours 103 mg. %, and three hours 60 mg. %. There was no glycosuria. The serum iron was 348μg. %, with an iron-binding capacity of 348μg. % (complete saturation). Chest x-ray revealed no significant abnormalities. An electrocardiogram was normal.

Course.—The patient was admitted to the Kaiser Foundation Hospital, in Los Angeles, on Nov. 11, 1956, at which time a transpleural needle biopsy of the liver was performed, confirming the clinical diagnosis of hemochromatosis (Figs. 1 and 2). After the patient was discharged from the hospital, weekly phlebotomies of 500 cc. were performed without difficulty. Occasional attempts to increase the amount or frequency of the phlebotomies were unsuccessful because of fatigue and depression, although no fall in the hemoglobin was noted at these times. A total of 28,300 cc.

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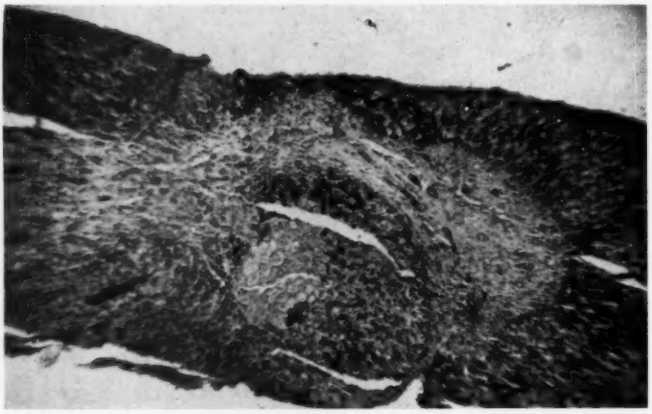

Fig. 1. — Histological section of a needle-biopsy specimen of liver, showing portal cirrhosis with abundant brown pigmentation, particularly in hepatic cells (low power).

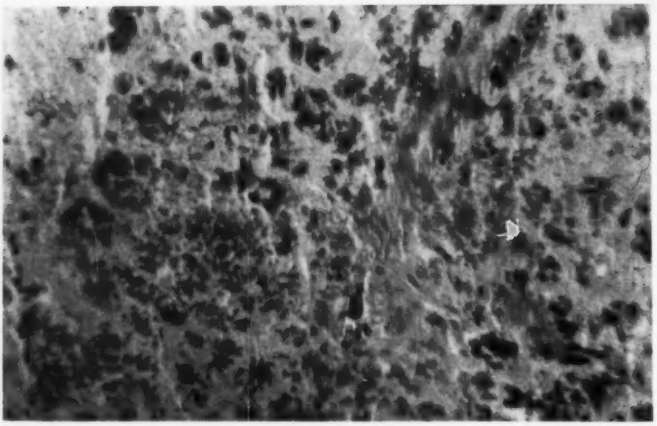

Fig. 2. — Histological section of the same biopsy specimen, with a stain for iron. The pigment is present in bile duct epithelium, connective tissue, hepatic cells, and Kupfer cells (high power).

of blood had been withdrawn by February, 1958, at which time the patient moved to another section of the country, where therapy is being continued. During the period of treatment she felt well and her hemoglobin remained between 12 and 14.6 gm/100 ml. There was gradual but definite decrease in the intensity of the cutaneous pigmentation, and the hepatomegaly regressed to 3 cm. below the costal margin. Laboratory studies were repeated on Jan. 27, 1958. The serum bilirubin was 0.8 mg. %. The total protein was 6.1 gm/100 ml.; albumin, 4.6 gm/100 ml., and globulin, 1.5 gm/100 ml. The cephalin-cholesterol flocculation was 2+ at 48 hours, and the thymol turbidity, 7.0 units. The sulfobromophthalein retention was now 1.5% at 45 minutes. The fasting blood sugar was 86 mg. %. The serum iron was 316μg. %, and the iron-binding capacity was 408μg. %.

Summary

A case of hemochromatosis occurring in a 39-year-old woman is presented. It is noted that this patient menstruated regularly and experienced menorrhagia until one and one-half years prior to the confirmation of this diagnosis, suggesting that she had a markedly increased intestinal absorption of iron.

Southern California Permanente Medical Group, 6440 Coldwater Canyon Ave.

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Acute Benign Pericarditis and Pneumonitis

Associated with Coxsackie Virus Group B, Type 2 Infection in a Young Man

LT. CMDR. JONAS SODE (MC), U. S. N. R., and LT. WILLIAM J. BAKER (MC), U. S. N.

Coxsackie viruses are widely distributed in nature and have been encountered in all parts of the world. They have been isolated from both sexes and from children more frequently than from adults. Isolations have been made from human feces, nasopharyngeal swabbings, the central nervous system, and the myocardium, as well as from sewage, cockroaches, and house flies.[1,2] γ-Globulin pooled from human sera neutralizes many Coxsackie viruses, indicating previous antigenic experience in wide population groups.[3] In fact, so ubiquitous is the distribution of Coxsackie viruses in humans, that their role as pathogens has been questioned until recently.

The Coxsackie viruses constitute a heterogeneous group of filtrable agents with different antigenic and histopathological capacities. It is as yet uncertain whether they represent a true family of viruses or several unrelated species with a common affinity for infant animal hosts. On the basis of histopathologic differences induced in suckling mice, 24 hours of age, two groups of Coxsackie viruses can be distinguished. Strains producing generalized myopathies are classified as Group A, whereas strains inducing inflammatory changes in the brain and the dorsal fat pad are classified as Group B. This classification is, however, more dependent on laboratory variables and less specific than one based on immunological criteria alone. Dalldorf,[4] utilizing neutralization tests, has identified 30 immunological types of Coxsackie viruses. Group B, which contains five distinct immunological types, grows in tissue cultures and is probably more pathogenic for man than is Group A. Group B viruses are generally considered to cause epidemic pleurodynia and some cases of aseptic meningitis. Group A, which contains 25 immunologically distinct types, has been shown to be responsible for herpangina and has been incriminated in meningoencephalitis. More recent reports have linked both groups of the Coxsackie viruses with single cases of benign idiopathic pericarditis [5,6] and acute idiopathic myocarditis.[1,2] Group B viruses have also been implicated in acute undifferentiated respiratory diseases occurring in seasoned and recruit military populations.[7] These reports indicate that the Coxsackie viruses are probably involved in the production of a wide spectrum of human diseases. Infections may occur in epidemic form, usually during the late summer. Interepidemic cases have also been documented and may constitute a human reservoir of infection.

The following is a report of a case of acute benign pericarditis and pneumonitis occurring in a young man infected with Group B, Type 2, Coxsackie virus. To the best of our knowledge, this represents the third case of pericarditis occurring in an adult in which a rise in antibodies to the recovered Coxsackie virus was demonstrated.[6] Furthermore, the rise in neutralizing antibodies in our patient was of sufficient magnitude to implicate the virus as an etiological agent.

Submitted for publication Dec. 8, 1958.

From the Medical Service, U. S. Naval Hospital, Great Lakes, Ill.

The opinions or assertions contained herein are the private ones of the writers, and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

Report of Case

A 23-year-old Negro man was admitted on Aug. 4, 1958, complaining of chest pain, dyspnea, and sweating. The patient had been in good general health until 30 hours prior to his admission, at which time he developed sudden and severe anterior chest pain while driving his automobile. The pain was sharp and stabbing, and there was radiation into the left shoulder, the left upper arm, and the upper abdomen. It was aggravated by deep breathing, coughing, and changes in position. The pain had persisted more or less unabated until admission, and there had been associated dyspnea and sweating.

The family history revealed bronchial asthma in the father and two siblings, diabetes mellitus in a grandmother, and heart disease of unknown type in a brother. The past medical history revealed the usual childhood diseases, bronchial asthma until the age of 3 years, two episodes of gonorrhea, and penile lesions at the ages of 19 and 20 years. The patient was prone to minor respiratory infections and suffered an average of five colds per year. Approximately three years prior to admission, he had been exposed to tuberculosis in a close friend, but follow-up studies had been negative. There was no history of rheumatic fever, scarlet fever, proven streptococcal infections, or chorea.

Physical examination revealed a well-nourished, muscular, and obviously vigorous Negro man in acute distress, complaining of severe anterior chest pain with radiation into the left shoulder and the upper abdomen. The patient was markedly dyspneic and sought relief by sitting up in bed and leaning forward. Marked splinting of the left hemithorax was noted, and a loud to-and-fro pericardial friction rub was heard to the left of the sternum and in the xiphoid area. The breath sounds over the left base were diminished, and bronchovesicular breathing was present below the left scapula. The physical examination was otherwise not remarkable. There was no pharyngeal injection or cervical adenopathy. The heart tones were of good quality; the venous pressure was normal, and the peripheral pulses were equal bilaterally and adequate. The temperature was 99.4 F; the pulse rate, 78 at rest, and the blood pressure, 140/90.

The admission hemogram showed a white cell count of 17,000, with 71% polymorphonuclear leukocytes, including 2 band forms, 22% lymphocytes, and 7% monocytes. The hemoglobin was 14.5 gm. and the hematocrit 48 vol. %. The corrected sedimentation rate was 15 mm. in one hour, with a rise to 30 mm. on repeat examination. The C-reactive protein test was negative, and repeated determinations of the serum glutamic oxalacetic transaminase were normal. Nose and throat cultures were negative for Group A streptococci, and the antistreptolysin O titer was 12 units. Blood serology, urinalysis, three blood cultures, three L. E.-cell preparations, multiple febrile agglutination tests, heterophil agglutination tests, and tests for cold agglutinins were noncontributory.

Skin tests with coccidioidin were negative, but positive skin tests were obtained with histoplasmin, purified protein derivative, and Frei antigen. Since the patient's past history was felt to adequately explain the positive Frei test, no serological studies for psittacosis-lymphogranuloma group viruses were performed.

The initial electrocardiogram showed RST-segment elevation in Leads I, II, aV_F, and V_4 through V_6, with depression in lead aV_R. Subsequent serial electrocardiograms revealed RST-segment elevation

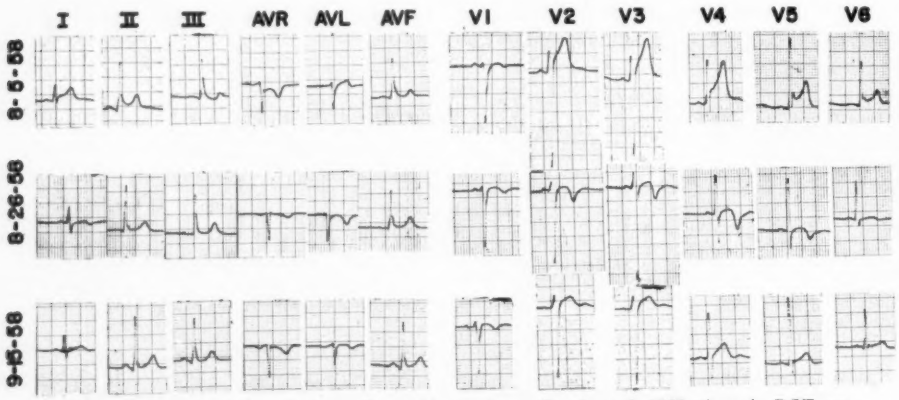

Fig. 1.—Representative electrocardiographic tracings. On Aug. 5, 1958, there is RST-segment elevation in Leads I, II, aV_F and V_4, V_5, and V_6 with aV_R depression. On Aug. 26, multiple T-wave inversions are noted. On Sept. 15, the tracing is normal except for remaining aV_L T-wave inversion.

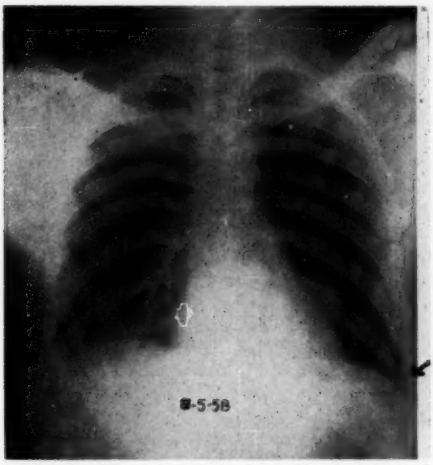

Fig. 2.—The admission chest film is pictured, with bilateral costophrenic angle infiltrates. The right side is more notable than the left. These had entirely cleared three weeks later.

in all precordial leads until Aug. 26, 1958, at which time multiple T-wave inversions were noted. Repolarization abnormalities persisted until Sept. 15, 1958, at which time the electrocardiogram became normal except for T-wave inversion in aV_L remaining. No subsequent changes were observed at rest and after exercise. Representative electrocardiograms are shown in Figure 1.

The admission chest film revealed pulmonary infiltrates bilaterally and a normal cardiac silhouette (Fig. 2). Subsequent chest-films showed gradual resolution of pulmonary infiltrates. No changes in cardiac size were noted throughout the entire series of chest films.

Throat and rectal swabs were obtained on Aug. 7, 1958, four days after the onset of symptoms, and inserted into screw cap vials containing gelatin lactalbumin-yeast extract maintenance medium. These were stored at —60 C until thawed for inoculation into HeLa-cell cultures. Group B, Type 2, Coxsackie virus was isolated from the throat swab.

Serum specimens were obtained on Aug. 7, Aug. 26, and Sept. 25, 1958. Neutralization tests were performed with use of 100 TCD_{50}* of the isolated homologous virus against serial dilutions of the patient's serum. The dilution containing the least amount of serum which completely inhibited all evidence of cytopathological changes in the HeLa cells was recorded as the end-point.† The progressive rise in neutralizing antibodies against Group B, Type 2, Coxsackie virus during the course of the patient's illness is shown in Table 1.

Serum protein electrophoresis was performed during convalescence at the time when the patient's neutralizing antibody titer was rising. The serum albumin was 58.2%; the α_1-globulin, 3.6%; the α_2-globulin, 8.8%; the β-globulin, 10.9%, and the γ-globulin, 19.0%.

* TCD_{50} represents the LD_{50} for this tissue culture, or the lethal tissue culture dose 50.

† Viral studies were performed at the Naval Medical Research Unit No. 4 by M. J. Rosenbaum, M.S.

Time Relationship Between Clinical and Laboratory Findings

	Wk. of Illness				
	1st 8/3-8/10	2d 8/10-8/17	3d 8/17-8/24	4th 8/24-8/31	8th 9/21-9/28
Chest pain	+++	Recurrence for 24 hr.	—	—	—
Dyspnea	++	—	—	—	—
Fever	99.4	—	—	—	—
Tachycardia on effort	++	+	—	—	—
Pericardial friction rub	++ for 36 hr.	—	—	—	—
Chest x-ray					
Lung fields	Bil. pneum.	Bil. pneum.	Min. resid.	Negative	Negative
Heart size	Normal	Normal	Normal	Normal	Normal
ECG	ST elevated	ST elevated		T-waves inverted	Normal; T aV_L invert.
WBC	17,000 12,800		7,500		
ESR/hr. (Wintrobe), Mm	15 26 30		18	15	8
CRP	Negative				Negative
SGOT, units	0	0		15 15	
Neutralizing antibodies for Coxsackie Group B, Type 2	8			16	32

The patient remained acutely ill for approximately 48 hours after admission and required narcotics for relief of severe anterior and left precordial chest pain which waxed and waned until Aug. 7, 1958. Subsequently, the hospital course was uneventful except for the recurrence of left-sided chest pain on the eighth hospital day. Treatment consisted of oxytetracycline, analgesics, and general supportive measures. The patient was allowed out of bed on Aug. 16, 1958, and, from that day on, his activities were slowly and progressively increased without any recurrence of chest pain, dyspnea, malaise, or cumulative fatigue. Serum glutamic oxalacetic transaminase determinations were repeated at the time of the development of deep T-wave inversion in multiple precordial leads, but no rise was demonstrated. In addition, the patient's circulatory response to the Valsalva maneuver remained normal. The patient was discharged to full duty after approximately six weeks of hospitalization, at which time the physical examination, chest x-ray, resting electrocardiogram, double Master's exercise tests, and ventilatory-function studies were considered to be within normal limits.

Comment

The diagnosis of acute benign or "idiopathic" pericarditis is usually made by exclusion of known causes of pericarditis. It does not, however, represent a specific disease entity, and it can be caused by a variety of etiological agents. The relationship of Coxsackie viruses to human disease has not yet been fully explored. That these viruses should be capable of producing pericarditis does not appear surprising when one considers the wide range of pathological changes that occur in experimental infections of animal hosts. The highly fatal myocarditis recently reported in infants infected with Coxsackie B virus [1] and the frequency with which involvement of the adjacent myocardium occurs in pericarditis of any cause cast some doubt on the benign nature of "idiopathic" pericarditis associated with Coxsackie virus infection.

The responsibility of deciding whether a virus is responsible for an illness in a given patient rests upon the clinician. Coxsackie viruses may be carried in human hosts for some time and may produce either clinical illness or inapparent infection. The mere isolation of these viruses from a patient does not, therefore, represent proof of a causal relationship. Kilbourne [8] has suggested certain criteria for the diagnosis of Coxsackie virus disease: 1. The clinical syndrome should be one of previously unknown or questionable etiology not associated with and not related to known pathogens. 2. An antibody response should be demonstrated to a virus of the Coxsackie group coincident with the patient's illness. 3. A Coxsackie virus should be recovered from the patient. According to Rhodes,[9] a fourfold or greater rise in neutralizing or complement-fixing antibodies during the course of a clinical illness indicates that the virus has proliferated to a considerable extent and is probably responsible for this illness.

The case presented meets the above criteria for the diagnosis of Coxsackie virus disease. The symptomatology, clinical course, and laboratory findings are in keeping with those reported in pericarditis by others.[10,11] The presence of bilateral pneumonitis in our patient is of interest. Pericardial friction rubs have been described in patients sick with viral pneumonias, and recent reports have linked acute respiratory diseases in military populations of the Great Lakes area with Coxsackie B infections.[7] Pleural and pulmonary involvement was frequent in previous descriptions of acute benign pericarditis.[10] In a series of 23 patients, pleural effusions occurred in 6 cases and parenchymal pulmonary infiltrates in 5.[11] The theory that contact transmission may occur has been considered.

It is of interest to speculate about the relationship between the increase in γ-globulin and the rise in neutralizing antibodies in this patient. Decreases in serum albumin and increases in α_2- and γ-globulin have been observed in infectious diseases, but the mechanism of these changes is unknown.[12,13]

Summary

A case of acute benign pericarditis and bilateral pneumonitis meeting suggested criteria for Coxsackie virus disease is presented. The history, the physical and

laboratory findings, and the clinical course are discussed.

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Paralyses of the Extraocular Muscles in Diabetes

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The neurological complications of diabetes have been extensively studied and recorded in recent years, especially peripheral diabetic neuropathy, characterized by loss of peripheral reflexes, hyperesthesia, paresthesias, nocturnal pain, and motor paralysis with muscular atrophy.[1] More recently manifestations of disturbed autonomic nerve function with loss of sweating and pilomotor control, orthostatic hypotension, tachycardia, pupillary abnormality, gastrointestinal motor disturbances, impotence, atonic bladder, and other sphincter disturbances have been described and emphasized.[2,3] Paralyses of the cranial nerves, though infrequent, have received less attention.

Three cases of paralyses of the ocular muscles seen in private practice within five years are reported. In the first case, the diabetic origin was not considered and the possibility of intracranial neoplasm or aneurysm was considered until the condition rapidly cleared. In the second case, the consultant rapidly recognized the presence of mild and as yet unrecognized diabetes. In the third case, diabetes had been poorly controlled for several years.

Report of Cases

CASE 1.—This 73-year-old man was found to have diabetes, in February, 1952. He was well regulated on 25 units of isophane (NPH) insulin and 1,800 Cal. diet, containing 180 gm. of carbohydrate, 80 gm. of protein, and 80 gm. of fat. He continued to be well regulated, with rare glycosuria and fasting blood glucose ranging from 138 mg. per 100 cc. to 124 mg. per 100 cc.

On Sept. 20, 1953, he developed diplopia. Five days later, on examination, he was found to have a blood pressure of 150/80. No abnormalities were noted in the optic fundi. The pupils were round, regular, and equal and reacted to light and accommodation. The left eye was weak on adduction and upward gaze, with double vision being noted by the patient. The other cranial nerves were normal, and no other abnormal physical findings were noted. These findings were confirmed by an ophthalmologist. A fasting blood glucose on this date was 108 mg. per 100 cc. Three weeks later he had evidence of complete paralysis of the left third nerve, with ptosis of the eyelid and downward and outward fixation of the left eye. On neurological examination there was questionable slight incoordination of the right lower leg, but no other abnormalities were noted. A fasting blood glucose examination on this date was 108 mg. per 100 cc. The urine showed no glucose when examined in the office several hours after the patient had eaten.

He was seen in consultation with a neurosurgeon, who noted the findings of paralysis of the left third cranial nerve but noted no other abnormalities. He concluded that the patient had a small vascular lesion in the region of the nucleus of the left third nerve. An aneurysm of the circle of Willis was considered, but direct surgical attack on this was deemed inadvisable until further diagnostic procedures, such as an arteriogram, were done. The paralysis gradually disappeared in about eight weeks.

He was seen one year later, and there were no abnormalities of the extraocular movements. The examination was again normal. A fasting blood glucose was 105 mg. per 100 cc. There was no glycosuria. The patient felt well and continued on the same dosage of insulin and the same diet. He has not returned for further examination but has continued to be well, without further illnesses. His daughter reports that he has no glycosuria and no further neurological symptoms.

CASE 2.—A 57-year-old man was in his usual state of health until Sept. 17, 1954, when he complained of dizziness and giddiness but no definite vertigo. No neurological abnormalities were noted on this date. The next day he complained of diplopia. Examination then revealed slight ptosis of the right eyelid and weakness on upward and medial downward gaze. His symptoms progressed so that his eyes deviated outward and downward, suggesting a complete third nerve paralysis. The pupil reacted to light and accommodation. About one year before this he had developed a moderate depression manifested by gastrointestinal symptoms. Complete x-ray examinations of the gastrointestinal

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tract revealed no abnormalities. Over the past year a small red "dot," which appeared to be a hemorrhage or a microaneurysm, was observed in the superior temporal area of the right optic fundus.

The physical examination was otherwise normal, except for the evidence of the paralysis of the third right cranial nerve.

He was seen in consultation with an ophthalmologist, who correctly surmised that the patient had diabetes. He noted, in addition to the hemorrhage mentioned above, a small flame-shaped hemorrhage and another microaneurysm in the fundus on the right. The visual acuity was normal, and it was noted that the patient's pupils were equal in size and reacted normally.

Urinalysis and complete blood cell count were normal. The serum cholesterol was 222 mg. per 100 cc. of blood. A fasting blood glucose was 104 mg. %. After 100 gm. of glucose orally, it rose in one-half hour to 178 mg. %, in one hour to 214 mg. %, in two hours to 147 mg. %, in four hours to 132 mg. %. Repeat gastrointestinal roentgenograms were normal. The patient was advised to lose weight and was given no other specific therapy, except for vitamins. A diagnosis of mild diabetes mellitus was made on the basis of the altered glucose tolerance.

The patient gradually lost 28 lb. Symptoms of diplopia and the objective findings of the paralysis of the eye muscles disappeared in seven weeks. Since then, the blood glucose has been within normal limits and the patient has never shown glycosuria.

About one year after this he developed symptoms of Parkinsonism in the right side that have been only partially controlled by drug therapy. In March, 1948, he underwent a prostatectomy successfully. He never showed glycosuria, and the blood sugar remained within normal limits. The hemorrhages and microaneurysms in the optic fundus have not been visualized since 1956.

CASE 3.—A 61-year-old widow noted about Nov. 10, 1957, the onset of "influenza," with fever, malaise, and aching. Eight days later she was examined, at which time she complained of pain in the left eye. On a brief physical examination no abnormalities of the eyes were noted, but two days later she was seen by an ophthalmologist, who noticed a slight weakness of the left lateral rectus muscle. The symptoms of diplopia progressed, but the pain subsided after about two weeks. At the onset the pain was very severe and was associated with lacrimation. She was again seen, one month later, and now marked paralysis of the muscle was noted. Because of a 4+ glycosuria she was advised to go into the hospital for further diabetic regulation. However, owing to the approaching Christmas holidays, she declined to enter the hospital at this time. She did enter on Dec. 27, 1957. By this time the weakness of the left lateral rectus muscle had greatly improved so that it was no longer obvious. Meanwhile, the diabetes remained poorly regulated.

In August, 1952, she had a myocardial infarction, complicated by congestive heart failure, from which she recovered, and she has been free of congestive heart failure since then. In 1954, she had symptoms of neuritis of the right thigh. In 1955, she was admitted to the hospital because of pain in the left hip. Roentgenograms of the involved region did not reveal any abnormalities at this time, and in a period of six to eight weeks this pain disappeared. In 1957, she was admitted for persistent burning pain in the distribution of the right 10th thoracic nerve. X-rays of the gallbladder, stomach, thoracic spine, and chest failed to reveal any abnormalities. This burning dysesthesia disappeared in about 10 weeks. Throughout this time her diabetic regulation has remained very poor, owing to her inability or unwillingness to follow prescribed diet and recommended insulin dosage. Her insulin dosage has remained between 60 and 80 units of isophane insulin each morning. While in the hospital she is easily controlled, and she leaves the hospital under good regulation.

On physical examination the blood pressure was 180/100. There was a weakness of the left lateral gaze. The optic fundi revealed normal disks, minimal evidence of hypertensive and arteriosclerotic changes, and a rare microaneurysm. The thyroid was slightly enlarged. There was a soft blowing systolic murmur, which was loudest at the apex. The chest was clear. The examination of the abdomen was negative. Neurological examination revealed the paralysis of the left lateral rectus muscle, which was less marked than 10 days before. The coordination was good, and the muscular strength was good. There were no sensory abnormalities, and the reflexes were equal and active. There were no abnormal reflexes. There were no sensory changes in the region of the right 10th thoracic nerve.

While in the hospital the patient was regulated and she was sent home on 70 units of lente insulin each morning. While she was in the hospital for 12 days, the weakness of the left lateral rectus muscle continued to regress. No other abnormalities were noted.

After discharge from the hospital the patient did well until about Jan. 20, 1958, when she developed a pain in the left lateral upper thigh. There was hyperalgesia to pinprick in this area, but the reflexes remained normal. This pain persisted for about two months and then disappeared.

Comment

In two of the cases, the third nerve was involved, with sparing of the pupil. In the

other, the sixth nerve was involved. In each case there was rapid but not sudden onset of the paralysis, associated with some pain. All recovered completely within a few weeks. The first case had relatively mild diabetes, was under good control, and did not change his diet or insulin dosage while under observation. The diabetes in the second case, a moderately obese middle-aged man, was so mild that it was demonstrable only by a glucose-tolerance test and was easily controlled by weight reduction. Glycosuria has never been demonstrated on repeated examinations, although a lesion consistent with a microaneurysm of the retina has been observed for one year. Ellenberg [4] presents a similar case, in which paralysis of the left third nerve was the initial manifestation in a patient with mild diabetes. The third case had poorly controlled diabetes and evidence of repeated attacks of sensory neuropathy in other peripheral nerves, all clearing within a period of two to three months.

In several reported cases there were repeated episodes of paralysis or bilateral involvement, all of which cleared.[5-7] In none of the reports reviewed was there failure of recovery of all the cranial nerves. The third and sixth are affected most commonly, and the fourth less often. The seventh nerve was mentioned,[8] but it would be difficult to separate the cases due to pressure within the canal of the facial nerve (Bell's palsy) from those due to diabetes. Only one report of involvement of the 9th, 10th, 11th, or 12th cranial nerve was found.[7]

Several distinct clinical features are worth emphasizing. There seems to be little correlation between the age of the patient or the severity of the diabetes,[9] although Weinstein and Dolger [10] thought the duration of the diabetes to be significant. In the second case, the diabetes was not recognized until the onset of the paralysis.

In involvement of the third nerve, the pupil is characteristically spared, a fact emphasized by Walsh,[9] though it may have been involved by preexisting neuropathy. The paralysis is usually accompanied by pain, often very severe, which may localize behind the orbit or spread to distribution of the first or second division of the trigeminal nerve of the involved side. The disappearance of the paralysis within a period of a few weeks to three months deserves repeated emphasis, since this feature would help to differentiate the condition from tumor or intracranial aneurysm, with which it is often confused. Furthermore, it seems to clear much more rapidly than the usual peripheral neuropathy.

There has been much speculation regarding the pathogenesis of this disorder. There has been less association of most of the reported cases with poorly regulated diabetes than is usually emphasized in reports of peripheral diabetic neuropathy. The characteristic complete clearing within three months further serves to differentiate it from certain features of peripheral and autonomic diabetic neuropathy, and for this reason it seems likely that the pathogenesis is not the same. Weinstein and Dolger [10] placed the lesion in the medulla oblongata in the region of the third nucleus, perhaps due to a small hemorrhage. Walsh [9] considered it probably due to involvement of the peripheral nerve outside of the brain stem. Recently, Dreyfus, Hakim, and Adams [11] had the unique opportunity of examining post mortem a patient with diabetes who had had a third nerve paralysis and who had died following arteriogram. They found a fusiform enlargement of the retroorbital part of the nerve. There was incomplete necrosis of parenchymal and interstitial tissue, with proliferation and evidence of early regeneration. The retention of pupillary constrictor function was thought to be explained by the fact that the peripheral part of the nerve, the site of these fibers, was less involved. Although the exact site of the lesion was not definitely identified, they considered the lesion compatible with an incomplete ischemic neuropathy, possibly due to an occlusion of a nutrient artery outside of the nerve. The pathologic changes observed could account for many of the puzzling features observed in other cases.

Recently Fagerberg [12-15] has presented a series of articles proposing that diabetic neuropathy is due, at least in part, to a specific angiopathy involving the vasonervorum, caused by infiltration of the vessel wall with a polysaccharide similar to that seen in vessels with retinopathy and nephropathy. In older persons, arteriosclerotic involvement of the larger vessels may also be implicated. There was evidence presented suggesting the specific lesion could be reversible.

Differential diagnoses of paralyses of the extraocular nerves include aneurysm of the internal carotid artery. The syndrome of pain in the eye or in the frontal or temporal region with oculomotor paralysis was considered by Dandy [16] and Jaeger [17] as almost pathognomonic of carotid or nearby aneurysms. The intracranial portion of the carotid artery is so close to the third, fourth, fifth, and sixth cranial nerves that any aneurysmal expansion or rupture of the vessel is apt to present symptoms referable to the eye. The fact that patients with diabetes have an unusually high morbidity following arteriography should be borne in mind before subjecting them to this procedure. The pain associated with the paralyses of the extraocular muscles in diabetes may be as severe as that produced by a ruptured intracranial aneurysm.

Most of the diabetic patients are in the fifth, sixth, or seventh decades, whereas aneurysms tend to occur in the younger age group. Diabetic retinopathy is usually present, and neuropathy in other areas may be found.

Neoplasm may produce similar symptoms. Meningioma of the sphenoid ridge and bleeding into a pituitary tumor have been recorded as producing ocular muscle paralysis.[18]

In thiamine deficiency, associated with chronic alcoholism, hyperemesis gravidarium, and occlusion of the stomach (e. g., by carcinoma), paralysis of the extraocular muscles may occur. Infections in cavernous sinus thrombophlebitis and chronic sphenoid sinusitis, with spread of infection to the base of the skull, is sometimes associated with involvement of the third, fourth, or sixth cranial nerve. Erosion of the tip of the petrous bone in chronic mastoiditis may lead to paralysis of the sixth cranial nerve (Gradenigo's syndrome).

Lesions, such as vascular occlusions, in the paramedian area of the midbrain may involve the third nucleus. Usually there is also associated contralateral hemiplegia (Weber's syndrome) or gross tremor (Benedikt's syndrome).

A leading textbook [19] states that oculomotor nerve paralysis due to involvement of the nucleus is rarely complete because the various components of the nucleus are spread over a wide area of the midbrain. Involvement of all of the muscles supplied by the third cranial nerve is almost certainly due to an infranuclear lesion.

In chronic syphilitic meningitis there is sometimes extraocular muscle paralysis. Paralyses of the extraocular muscles occur occasionally in the Guillain-Barré syndrome and rarely in poliomyelitis but usually not as an isolated feature.

Ophthalmoplegic migraine is a rare entity. It is usually seen in children and is characterized by recurring episodes of nausea, vomiting, pain over one side of the head, with ophthalmoplegia which remits as the child grows older. The age of onset would serve to differentiate it from the cases reported here.[18]

Summary

Three cases of paralysis of the extraocular muscles occurring in patients with diabetes mellitus are presented. In two, the third and, in one, the sixth cranial nerve were involved. In each, recovery was spontaneous, and all had complete return of function in a few weeks. In the first case, the diabetes remained well controlled on the same insulin dosage. In the second case, the initial manifestation of the diabetes (except for questionable retinopathy) was the ophthalmoplegia. The third case, who had had poorly controlled diabetes for years, had had previous episodes of peripheral neuropathy.

She recovered from the ocular paralysis in spite of continued poor control of her diabetes.

The syndrome of ocular paralysis occurring in diabetes is characterized by weakness of the muscle innervated by one nerve, usually the third. Pain in the involved eye or side of the face is usually present and is often severe. The pupil is characteristically not involved. Recovery is complete in a few weeks.

The pathogenesis is apparently due to an ischemia of the nerve due to a lesion of the vasonervorum. Recent evidence suggests that this may be a specific angiopathy related to the retinopathy and nephropathy.

Differential diagnoses include intracranial aneurysms, neoplasms, various vascular lesions, and other rare causes of paralysis of the extraocular muscles.

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Evolution of Modern Medicine

This section, which has as its primary purpose a review of the contributions of medical investigators and observers of the past to the present-day concepts of disease, is under the special editorship of Dr. Arthur Bloomfield, 2398 Sacramento St., San Francisco 15.

His editorial in the August, 1957, issue of the A. M. A. Archives of Internal Medicine, *gives further detail of what it is hoped to accomplish in these articles. Contributions or comments for this section may be sent directly to Dr. Bloomfield, or to the Chief Editor for transmittal to him.*

Medical Research from Harvey to Harrison

WILLIAM DOCK, M.D., Brooklyn

The following essay, which stresses some neglected highlights of development of our present knowledge of the circulation, is interesting also because in it a distinguished internist of America receives a gracious tribute from a distinguished colleague. The occasion was the first Tinsley Randolph Harrison Lecture of the University of Alabama. The address was delivered Nov. 25, 1958, at the Medical College in Birmingham. The lecture was founded by colleagues, pupils, and former house officers, led by Dr. Robert Williams, of Seattle.

P. S. R.

In Birmingham one could well say to those who ask about a memorial to Tinsley Randolph Harrison: "Look around!" The changes in the physical plant of the Alabama College of Medicine and its associated hospitals is visible proof of his activities in recent years and will long remain as a monument to his influence on the school. The library will preserve copies of his pioneer book on the failure of the circulation in addition to his textbook of medicine, both highly respected in many lands as well as in America.

Far more important has been his effect on the care of patients, on the policies in medical education, and on the collaboration of laymen and physicians in seeking to solve medical problems. As an active member of the American Heart Association he pushed this collaborative effort, and as president of the Association he inaugurated the program of support for research and for capable investigators, which, in the past ten years, has increased the annual research appropriation of the Association to a level of $2,500,000. However, the lectureship inaugurated tonight is a tribute to still another aspect of this compact human power plant.

Dr. Harrison's greatest contribution to American medicine has been his zeal in leading capable young men to devote much of their time to medical investigation. The present places in the medical life of our country occupied by these men, some his own age and some half his age, supply the best evidence of his success in kindling fires in inflammable material. At the dinner in his honor last spring, his disciples, from Professor Blalock, at Johns Hopkins, to Professor Williams, from Seattle, gave eloquent testimony to his role in starting these men in a direction which has given them professional satisfaction as well as great reputations.

It therefore seems worth while tonight to examine a part of the history of a field of medical research dear to Dr. Harrison, with a view to clarifying what medical research

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demands of its followers and what it offers them.

Medical research, or investigation, or what Thomas Lewis called clinical science, is very different from careful observation of disease, or of the anatomy, or of functions of the human body. Vesalius' dissection of human bodies and his beautiful book on anatomy, Heberden's classic description of angina pectoris, and even Jenner's finding of coronary artery disease in patients with angina cannot be considered examples of research. However, Jenner's study of cowpox and prevention of smallpox by vaccination and Withering's report on the effects of foxglove leaves in heart disease are typical of the planned series of experiments which comprise research in medicine.

The history of medical research on the function of the heart does not begin with Vesalius' anatomical work or with the guesses of Colombo and of Servetus that blood flowed through the lungs from the right side of the heart to the left. Nor does it begin with Cesalpino's thesis, craftily concealed from the Inquisition in a book on botany, that blood flows through innumerable invisible channels or capillaries in the most solid tissues of the body, passing first through the lungs, then through the rest of the body, and back to the heart. Cesalpino's views, and those of Colombo and Servetus, certainly were known in Padua, where Harvey studied under Fabricius, a successor of Vesalius. Fabricius' discovery of valves in veins and his interest in the mystery of reproduction fell on fertile soil and inspired Harvey's life work, but Fabricius did not conduct any experiments in these fields.

Harvey never proved that there was a double circulation in man, and he convinced few physicians with his lectures, his book, and his letters in support of that theory, but he did conduct many planned experiments on growth and on the circulation, and he did collect a good deal of circumstantial evidence in favor of the circulatory theory. He did not realize that the heart was merely a pump but ascribed to it many noble functions as the key organ in purifying and fortifying the blood. This was the view held by the medical world for two thousand years, and it was accepted by Harvey.

To most doctors, including Sydenham, the great physician of the generation taught by Harvey, there was no practical application of Harvey's view. Therefore, it was easy to ignore it or to reject it as a heretical attack on Galenical medicine, revered alike by Islam and Rome. After Malpighi had observed blood corpuscles with the microscope and found them flowing in only one direction in the tissues, the vociferous objections to Harvey were quietly dropped by the Italian and French physicians who had most insultingly criticized him.

To me, the most extraordinary thing about Harvey was his belief that experiments on snakes and chicks growing in eggs would be taken seriously by physicians interested in that noble, almost divine, and certainly immortal creature, man. Only this year I heard a great professor, a graduate of Harvey's own University, publicly insist that dietary regimens which produce arteriosclerosis in rabbits, chicks, dogs, rats, and apes cast no light whatever on arterial disease in man. We therefore cannot praise too highly the confident assumption of Harvey that experiments on animals probably will give useful and dependable information on the functions and diseases of human organs.

Harvey, who ascribed purifying and fortifying actions to the heart, was content to suggest flow rates as low as 170 ml. per minute, and his upper limit was 1,200 ml. per minute. This guess was steadily increased in the next three centuries. Finally, in 1928, W. F. Hamilton and J. M. Kinsman, of Louisville, invented the dye-dilution technique for measuring flow through the lungs and for the first time obtained an accurate figure, 5,000 ml. per minute. Harvey, the wild radical, turned out to have been very conservative indeed about the volume of blood pumped by the heart.

The crucial experiment on the circulation was performed by Richard Lower, a country doctor in Cornwall, the windy southwest

tip of England, at about the time that the microscope revealed to Malpighi the red blood cells streaming, always in one direction, through the capillaries in animal tissues. Lower took lungs from freshly slaughtered beasts and poured blue venous blood into the artery. When it ran freely and unmixed with air bubbles, but now bright red, out of the pulmonary veins, he had demonstrated the existence of the channels imagined by Cesalpino and Harvey and proved that it was not an action of the heart but exposure to air in the lungs which was needed to convert blood from venous blue to arterial red. A Cornish colleague of Lower's, John Mayow, was interested in chemistry. He showed that the gas obtained from nitrates, or "nitroaerial spirit," turned venous blood red. This gas we now know as pure oxygen, while air is only twenty per cent or, perhaps in Kentucky forty proof, oxygen.

We have now come to the closing decades of the seventeenth century, a period of rapid progress in physics, thanks to Newton, Boyle, and the other founders of the Royal Society. More than a century passed after Lower, Mayow, and Malpighi had established the reality of the circulation through the lungs and the effects of simple aeration of blood before the true role of the heart, lungs, and the red blood corpuscles was actually discovered. It was only on the eve of the French Revolution that the real explanation of what happened when blood turned blue in the tissues of the body and red in the lungs burst on an astonished and incredulous medical world. This overthrew the theories of Stahl on metabolism, combustion, and inflammation, which all eighteenth-century scientists and physicians had accepted as gospel. The steps which led to this revolution were due to two British clergymen and a French business man and millionaire. In this most important research on the function of the heart, lungs, and circulation, physicians played no part whatever.

We can confidently say that if Stephen Hales, like Harvey, a graduate of Cambridge, had not lived or had not had the Church positions which gave him time for research, Priestley would not have been able to make his great contribution to the study of gas exchange by plants and animals. Priestley also was a preacher, a Presbyterian who turned Unitarian and eventually fled to Philadelphia. The studies he made in his home proved that light was necessary for green plants to produce the gas which made air beneficial to animals. Without Hales' techniques and Priestley's discoveries, Lavoisier would not have been able to lay the foundations of modern chemistry and industry. Thus, to the lively rector of various eighteenth-century rural parishes we owe the fact that we are, for better or worse, at least half a century ahead in the development of the modern world. Medicine and industry today would be about where they were when Osler left Baltimore to go to Oxford, in 1905, if this extraordinary genius had not made his startling discoveries before 1730. All the money England paid to support the Anglican clergy, from Henry the Eighth to our Elizabeth, would be justified by the accomplishments of this scholar, but this system of subsidizing gracious leisure produced many other additions to our knowledge of science, history, and the humanities. For this system, like the Established Investigator program of the American Heart Association, gave men like Hales the opportunity to devote five days a week to their own studies.

Stephen Hales' work on plants and animals soon led to his entrance into the Royal Society and to a two-volume report of quantitative studies on metabolism and flow of sap in plants and the flow and pressure in blood vessels of animals. He holds a high place in the histories of botany and of medicine, but in the medical histories his main contribution, because indirect, is never mentioned.

For the serious student of the history of physiology, it is not Hales' studies of the rate of flow and the pressures in the blood vessels which are of greatest importance, even though he was the first to measure the

arterial blood pressure of an animal. All his work on these problems showed great ingenuity and care but contributed nothing to the solution of the great mystery, what is the purpose of the circulation? His work on how trees and plants are built up out of thin air held the key to that problem. Hales was the first to produce evidence that plants are built up of solid substances formed out of water and a gaseous substance taken from the air. He first suggested that light "which makes its way into the outer surfaces of leaves may contribute much to the refining of the substances in plants."

Using Hales' techniques, Priestley proved that, in the light, green plants produced a gas which supported the life of animals even better than air. Priestley used the survival time of a mouse, enclosed in a jar of gas, to test its "goodness." Lavoisier showed that "goodness" was due to a gas (Mayow's "nitro-aerial spirit") which he named oxygen. He proved that animals burn carbon compounds, sugar and fat, only in oxygen, just as does a candle and that the heat these animals produce has the same relation to the oxygen used and the carbon dioxide produced as does the heat given off by a wood fire or by a candle. He also proved that plants take up carbon dioxide, converting it to oil or sugar, and give off oxygen. All these experiments, which proved that the role of the circulation is to carry oxygen from the lungs to the cells of the body and bring back carbon dioxide from the cells to the lungs, were carried out with the simple device Hales had invented, the pneumatic trough.

Toricelli, Boyle, and others who studied the vacuum above the mercury in a barometer or produced by air pumps, and who began the study of gases, were baffled by the problem of handling and measuring gas given off or used up in combustion and other chemical reactions. Hales solved this by inverting a water-filled beaker in a bowl of water and leading a tube from the closed reaction chamber under the edge of the water-filled beaker, so he could collect and measure any gas given off. By floating plants or animals on the surface of the water, after introducing air or gas into the beaker above the level in the bowl, he could study changes in volume and quality of the gas or air due to vital activity. Hales' ingenious method, with his control beaker to follow and correct for the volume changes due to temperature or barometric variations, was used by all his successors in studies of respiration of plants and animals.

After 1800, thanks to the work of these pioneers, it was clear that the only function of the heart was to pump enough blood to keep the tissues supplied with oxygen and free of accumulated carbon dioxide. Seventy years went by before Fick suggested the obvious fact that, if one divides the gas taken up or given off by the lungs in one minute by the difference in gas content of arterial and mixed venous blood, the figure obtained is the volume of blood flowing through the lung each minute. After another fifteen years, Gréhant and Quinquaud finally applied this and measured pulmonary blood flow in animals. Then thirty-five years more passed before Dr. Harrison, then in Boston, applied this technique to measurements of the changes in blood flow of dogs and rabbits due to experimental disorders such as collapse of a lung or a large leak between an artery and vein.

In 1929, Forsmann reported that he had slid a tube into an arm vein and right into his own heart without any ill effects. He was interested in injecting drugs through his tube, but Klein, in Prague, saw that this was the way to get mixed venous blood in man, as Gréhant and Quinquaud had in horses and Harrison had in dogs and rabbits, directly from the right ventricle of the heart. In 1930, he gave the first figures for human blood flow determined by the Fick principle and by right heart catheterization. Twelve years later, Cournand, Ranges, and Riley, on a government contract to study shock, applied this method to normal and diseased men. Three hundred thirty years after Harvey began to preach the circulation to the men in his anatomy

class, the determination of cadiac output in man became a routine diagnostic procedure.

The essential steps in establishing the rationale as well as the existence of the circulation were by-products of the study of botany. Cesalpino, studying the enormous rate of flow of sap through the apparently solid substance of trees and plants, postulated similar channels, the capillaries, carrying blood through the apparently solid but much softer tissues of our bodies. Fabricius noted valves in veins which only permitted flow toward the heart, but only a man like Harvey, living in a country of heretics with no fear of the Inquisition, dared defy authority and expand the knowledge Cesalpino and Fabricius had provided. While Lower and Mayow proved that blood flowing through the lung or exposed to air, or the gas held by nitrates, turned from blue to red, it was the work of Hales, Priestley, and Lavoisier on gases and the metabolism of plants which finally explained what the circulation did and why the minute flow had to be far greater than Harvey dared to suggest.

The fact that in the study of the circulation the key discoveries came from men studying plant physiology should be borne in mind whenever one discusses how to solve the problem of cancer, of aging, or of any of the profound mysteries which confront doctors today. Only those physicians who are students of general biology—of plants as well as animals—are likely to make any really fundamental contributions to our knowledge of the human body or to our ability to prevent or control disease. Major contributions will always come from biologists, from physicists, or from chemists who, like Pasteur, become fascinated by biology, or from physicians who have equally broad interests and training. This fact was stressed by Tinsley Harrison when he guided the Research Committee of the American Heart Association, whose beneficiaries need not attack immediate problems but study whatever phases of science seem attractive. Nature yields her deepest secrets not to those who confront her with a blunt question on a single topic but to men or women whose lives are spent in the admiring study of all her beauties and mysteries.

For the most part physicians who engage in medical research have immediate, rather simple, problems to solve and realize that they are not equipped to make any great discoveries. As scientific study has expanded in the last four centuries, it has become apparent that no problem ever is solved but that each advance in learning reveals new paths leading deeper into the great mysteries of the universe. Yet each advance in a fundamental discipline opens up new ways of exploring old problems and often makes possible the solution of practical questions in many fields. Most physicians engaged in research, like Harvey and Harrison, are seeking evidence to support ideas advanced by others with a wider and deeper interest in all life processes or are applying to patients techniques supplied by chemists or physicists—by men like Roentgen, who gave us the x-ray, or Henri Becquerel, who gave us radioactivity and isotopes for tracing chemical processes in the body. While the research done by physicians is not very original, it is of utmost importance to patients, since it does increase the accuracy of diagnosis and the effectiveness and safety of treatment.

Even among the physicians who take an active interest in research, few continue to do experiments all their lives, as Hales, Harvey, and Pasteur did. Occasionally, a man who has been some years in practice and has shown no interest in research develops an obsession to explore a medical problem and starts to do research. Some of these men are soon discouraged, while others go on for years with no significant result. A rare and fortunate practitioner, like Frederick Banting, falls in with men with the right outlook and training and makes a very great contribution, as he did in discovering insulin with Best, a medical student, and Collip, a professor of biochemistry. Rarest of all are the practitioners, like Robert Koch, who train themselves in

a fundamental technique and make a brilliant career in research.

The great bulk of useful work in medical research at the practical level has been done by those who turned to this field as medical students or interns, fired by something in a textbook, a lecture, or a patient and encouraged or inspired by teachers like Fabricius or Tinsley Harrison. Many such curious students have done fine work before the age of thirty and then have become fully and happily engaged in practice. A few have devoted all their mature years to teaching or administration, interested in the research of others but not in continuing to do experiments themselves. Two examples of those who had no interest in research as a career, but enjoyed experimental work in the salad days before practice, are Dr. Goodale, of Boston, who developed the technique of coronary vein catheterization and measured blood flow in the human heart muscle, and Dr. Samuel Grant, of St. Louis, who measured the effect of chilling the skin on blood flow in the lining membranes of the nose and throat and discovered the alkalosis and tetany of overbreathing while he was still in medical school. As a house-officer in Boston, he first proved that insulin restored to the body tissues the power to burn glucose. It was Grant who inspired Harrison and turned over to him the laboratory he had developed for study of blood flow by the Fick principle. Goodale and Grant had as their objective the noble profession of family physician. They did research for the love of it when they saw problems and the opportunity to solve them while preparing to enter their chosen field. At the time Tinsley Harrison measured blood flow in rabbits, his only ambition was to be a good family physician in Birmingham, but in his forty years of wandering in the academic wilderness he has passed on to many colleagues and pupils the research "bug" contracted in Boston.

Very different in motivation, but not to be scorned as far as their useful contributions are concerned, are those who have no great interest in research or medical discovery but realize that this can provide the way to a professorship or an important executive position or establish a reputation as a specialist. Such men stop research as soon as they achieve their real objective. We all know some recent examples of important contributions made by this group, of which Vesalius furnishes the classical example.

He burned with a desire to be a court physician to the Emperor of Austria and Spain and shrewdly perfected himself in anatomy, became professor at Padua, published his marvelous book in Basel, and at thirty reached the sought-for goal. Thereafter, he trailed after the court and published a book on sarsaparilla as a specific for syphilis, then rampant among nobles as well as common folk. He offered sour and incorrect criticisms of the anatomic discoveries of his successors, but just as Michelangelo did superb work in filling orders for Popes and Medicis, Vesalius and many since his day have done fine work in medical exploration while seeking other objectives. Motivation, in research as in the arts, is of less importance than a lively mind, sound judgment, and a capacity for taking pains. A great deal of poor work in medical research has come from men with noble intentions, but poor judgment, careless habits of work, or no real feeling for Nature.

Medical advances of significance have been made by men seeking fame, position, or power. These are men with brains and energy but little love of Nature, the attribute which chiefly distinguishes those who continue in productive research all their lives and especially those who have made the most original contributions. A recent example was the late Frank Wilson, of Michigan, who laid the sound foundation for modern electrocardiography. He was equally and deeply interested in astronomy, in birds and their nesting habits, in gardens, in wild flowers and forests, and in his associates and patients.

Since I have chosen to point out men whom we rate very highly as investigators, it may well be asked, "How do you evaluate the performance of men in research?" The

work itself can be considered only after it has been confirmed by others, and so snap judgment is often erroneous. When the investigator is one of a team, only his teammates can judge, but his subsequent contributions, compared with that of the others on the team, often provide circumstantial evidence. We judge the merit of accomplished and tested work by a relatively simple formula. Accomplishment divided by opportunity gives us the true value of an investigator. A modest advance made by a medical student, a busy teacher, or a practitioner may be as meritorious as a great discovery obtained by a team of full-time investigators with the enormous resources of a great research foundation. Looking back over a decade or two of work, we take little satisfaction from our contributions to problems which occupied half a dozen of our colleagues at the same time, even if we arrived at correct answers a little ahead of them. What really pleases us is work done on a problem which interested no one else when we began but which later became a topic of lively interest. What saddens us is to find that our methods were clumsy; our ideas, sterile, or our conclusions, erroneous. However, even the greatest of the pioneers made laughable errors, wasted time on false clues, or used complicated ways of doing something which later was done simply. No one can do much research without having similar experiences, but we must balance the ratio of hits to errors.

Today, enormous amounts of money are available to support research, and much of it is used to keep the investigator free from the daily chores of teaching, preaching, or administration, which all the great investigators in the history of science took for granted as a normal part of their lives. Not enough money is spent on providing good teachers at the grammar-school and high-school levels, where, in many cases, the sparks of a brilliant mind are buried in the ashes of uninspiring teachers and classmates. For the difference between competent investigators and brilliant pathfinders is due to inherited superiority of mind and favorable environment in childhood and youth. The favorable environment is one which awakens an attitude of awe and curiosity toward the Universe and all its living creatures, and this awakening comes from parents, teachers, and friends. No amount of money spent for research institutions and full-time positions will increase the number of brilliant investigators.

When we have reviewed the history of any field of scientific endeavor, we realize the full meaning of Coleridge's lines:

> He prayeth best who loveth best
> All things, both great and small.

For it was a frail sprig of peppermint and a tiny mouse which gave mankind the secret of the growth of plants and of the production of heat and energy by animals, engines, and explosives. The men who were awarded the Nobel prize in medicine this year, for making an incredibly great advance in our knowledge of heredity, used for their experiments the minute organism which makes bread mouldy. The greatest professional satisfaction and the greatest contributions to human understanding come to those whose early years have led them to realize the creed so nobly described by the Polish novelist and sea captain, Joseph Conrad:

> An unwearied self-forgetful attention to every phase of the living universe reflected in our consciousness may be our task on this earth—a task in which fate has perhaps engaged nothing of us except our conscience, gifted with a voice in order to bear true testimony to the visible wonder, the haunting terror, the infinite passion and the illimitable serenity; to the supreme law and the abiding mystery of the sublime spectacle.

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Contributions of Basic Science to Modern Medicine

Serotonin and the 5-Hydroxyindole Pathway of Tryptophan Metabolism

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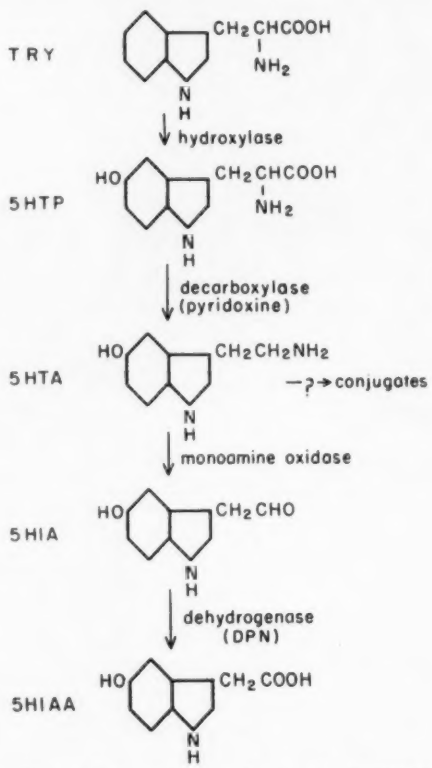
The presence of a vasopressor factor in clotted defibrinated blood has been known for 90 years. This factor, serotonin, was isolated from blood platelets and identified as 5-hydroxytryptamine in 1948, by Rapport. In 1937, enteramine, a smooth muscle constrictor which was later found to be identical with serotonin, was isolated from intestinal mucosa by Erspamer. He suggested that enteramine was a hormonal substance secreted by the argentaffin cells of the intestine. Intense interest in this entire subject was stimulated by recognition of the disease entity, malignant carcinoidosis. The syndrome is caused by malignant carcinoid tumors (argentaffinomas), which contain large quantities of serotonin. Patients with carcinoidosis have increased amounts of serotonin in the blood and large quantities of 5-hydroxyindoleacetic acid, the major metabolite of serotonin, in the urine. The clinical features of the carcinoid syndrome include episodic flushing of the skin, patchy cyanosis, telangiectasia, pellagra-like skin lesions, bronchoconstriction, edema, atypical valvular heart lesions, abdominal cramps, and diarrhea. Exhaustive reviews of serotonin [1] and carcinoid disease [2] have recently appeared. It is the purpose of this paper to describe the metabolic pathway involved in serotonin biogenesis and catabolism and to discuss briefly aspects of this pathway which may prove to be of clinical interest.



The 5-hydroxyindole pathway of tryptophan metabolism.

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Present understanding of the 5-hydroxyindole pathway of tryptophan metabolism is summarized in the Figure. Tryptophan is apparently hydroxylated to form 5-hydroxytryptophan (5-HTP), or serotonin precursor, which is then rapidly decarboxylated to form 5-hydroxytryptamine (5-HTA), or serotonin. In the presence of monoamine oxidase 5-HTA undergoes oxidative deamination to form 5-hydroxyindoleacetic acid (5-HIAA), which is excreted in the urine. This concept of the formation and degradation of serotonin, the relationship of this pathway to the carcinoid syndrome, and practicable methods of measuring 5-hydroxyindole compounds in biological media have been largely the result of a series of excellent investigations by Udenfriend and his associates.[3-8]

Tryptophan Hydroxylation

There is considerable evidence to suggest that tryptophan is the dietary precursor of serotonin. Administration of tryptophan orally to patients with malignant carcinoidosis does not regularly result in an increased urinary excretion of 5-HIAA, although deprivation of tryptophan may result in decreased amounts of 5-HIAA in the urine.[9] It is not yet agreed whether a significant increase in urinary 5-HIAA excretion can be demonstrated in normal humans or animals after tryptophan administration. When isotopic carbon (C^{14})-labeled tryptophan, however, is administered to patients with carcinoidosis, 5-HIAA containing the C^{14} label can be recovered from the urine.[10] Hydroxylation of tryptophan to form 5-HTP has been demonstrated in the bacteria, Chromobacterium violaceum, and in the toad.[11] Direct demonstration of this reaction in mammalian tissue, however, has not yet been possible.

It would appear that the hydroxylation of tryptophan occurs very slowly and probably represents the rate-limiting reaction of the pathway of 5-hydroxyindole metabolism. The site of this reaction remains unknown[12]; however, it would be reasonable to suspect that tryptophan hydroxylation may occur only in certain specialized cells, of which the argentaffin cell would be an example.

Although probably no more than 1% of dietary tryptophan is normally metabolized by means of the 5-hydroxyindole pathway, it appears that patients with carcinoidosis may convert as much as 60% of dietary tryptophan to 5-hydroxyindole compounds.[13] This shunting of tryptophan into the 5-hydroxyindole pathway may diminish the utilization of tryptophan for the formation of protein and nicotinic acid. This may explain the clinical features of pellagra and the decreased amounts of urinary N^1-methylnicotinamide observed in some patients with carcinoidosis.

Decarboxylation of 5-Hydroxytryptophan

Numerous in vitro and in vivo studies suggest that 5-hydroxytryptophan is the immediate precursor of serotonin. There is no evidence, on the other hand, that tryptamine is hydroxylated to form serotonin. For every 2 mols of serotonin precursor incubated anaerobically with mammalian tissue, 1 mol of 5-HTA and 1 mol of CO_2 are formed. This observation may be explained by recent studies suggesting that only the *l*-form of 5-hydroxytryptophan is normally decarboxylated to form serotonin.[14]

Administration of serotonin precursor to animals results in a significant increase in the serotonin content of platelets, liver, spleen, gastrointestinal tract, and brain,[4] usually reaching a maximum in one to two hours and lasting six to eight hours. Since sustained increases in tissue serotonin levels can be obtained with its precursor, and since this compound passes the blood-brain barrier, 5-hydroxytryptophan administration may often be a more useful experimental tool than the injection of serotonin itself, which does not enter brain tissue and which causes only transient rises in the serotonin concentration of other tissues. The administration of 5-hydroxytryptophan, in addition to increasing tissue serotonin, results in an increased urinary excretion of

5-HIAA in man and experimental animals. In general, about 30% of the administered *l*-form of 5-hydroxytryptophan may be recovered in urine as 5-HIAA,[8,15] although recoveries of 5-HIAA greater than this have been noted in patients with decompensated hepatic cirrhosis.[15] As much as 10% of administered serotonin precursor may be recovered in the urine as 5-HTA.[8,15]

Since the formation of 5-HTP from tryptophan occurs very slowly and since decarboxylation of 5-HTP appears to be rapid and complete, it is not surprising that this compound has not as yet been isolated from normal mammalian tissue or excretions. However, 5-HTP has been identified chromatographically in the urine of one published case of malignant carcinoidosis [16] and in the urine of a carcinoid patient studied in our laboratory. In both cases the tumor cells closely resembled the typical argentaffin cell but did not have the cytoplasmic argentaffin granules usually seen. It is not known whether some carcinoid tumors may secrete 5-HTP which is then decarboxylated elsewhere in the body to form 5-HTA.

The decarboxylation of 5-HTP is catalyzed by a specific decarboxylase. Activity of this enzyme has been demonstrated in vitro in mammalian kidney, liver, gastrointestinal mucosa, brain, and lung and in carcinoid tumors. A relatively pure form of the enzyme has been isolated from guinea pig kidney.[5] Decarboxylation is apparently inhibited by hydroxylamine and semicarbazide, indicating that pyridoxine (vitamin B_6) is a coenzyme. Diminished formation of serotonin from its precursor has been demonstrated in vitro in the kidney of pyridoxine-deficient rats [17,18] and in vivo in pyridoxine-deficient chicks.[17]

Diminished 5-hydroxytryptophan decarboxylation and a resulting deficiency in serotonin have been suggested as a possible cause of the mental defects observed in phenylketonuria. Inhibition of guinea pig kidney 5-hydroxytryptophan decarboxylase activity by phenylacetate and related compounds has been described.[19] Since these compounds tend to accumulate in phenylketonuria, inhibition of 5-hydroxytryptophan decarboxylation has been suggested as a basis for the low urinary excretion of 5-HIAA observed in patients with this disorder.[20]

Serotonin

The biologically active compound which is formed as a result of tryptophan hydroxylation appears to be serotonin (5-HTA). This compound is widely distributed in nature and has been identified in such diverse entities as bananas, various venoms, and certain mushrooms. In mammalian organisms the chief, but probably not the only, source of serotonin is the argentaffin cell. Whether these cells secrete serotonin or merely synthesize serotonin precursor (5-HTP) has not yet been established. The tissue mast cells of rats and mice have been shown to contain serotonin and to be capable of decarboxylating 5-hydroxytryptophan.[21] Large amounts of serotonin have been found in transplantable mast-cell tumors of mice, and animals with such tumors excrete excessive amounts of urinary 5-HIAA.[22] As yet, there is no evidence that the tissue mast cells of other mammalian species, including man, contain serotonin.

While there have been several reports of the 5-HTA content of various mammalian tissues,[23-27] little is known about the distribution of serotonin in man. In the species thus far studied, the largest amounts of serotonin are found in gastrointestinal mucosa, blood platelets, spleen, brain, and lungs. Recent evidence suggests that serotonin is concentrated in the mitochondria. It is presently thought that 5-HTA is active only in the free form; with binding to tissues or platelets, the compound apparently loses biological activity. At least no functional activity of 5-HTA in the bound form has been demonstrated. The mechanism by which 5-HTA becomes bound remains undefined. Studies by Born et al. suggest that adenosine triphosphate may be concerned with the binding of 5-HTA to platelets.[28]

The serotonin formed in various tissues is apparently released into the blood, where it is rapidly taken up by platelets. Exogenously administered 5-HTA is similarly bound by blood platelets. That platelets are not fully saturated with 5-HTA is suggested by the fact that normal platelets are capable of taking up serotonin in vitro from an incubation medium. The blood content of serotonin varies considerably from species to species. Normal human whole blood contains only 0.1μg.-0.3μg. per milliliter of serotonin, while values of 4.0μg. are obtained in rabbits. It would appear that platelets merely absorb serotonin in some manner; there is no evidence that they are capable of synthesizing or degrading serotonin. With platelet disintegration there is release of serotonin into the plasma. Under certain circumstances, however, liberation of the compound from platelets is possible without their destruction. There has been no definitive demonstration of a role for serotonin in platelet function or hemostasis.

Serotonin is readily released from blood platelets and brain during anaphylaxis and after reserpine administration.[29,30] Release occurs much less readily from the gastrointestinal mucosa and from carcinoid tumors. The mechanism of serotonin release is not understood. It has been calculated that hundreds of serotonin molecules are released by one molecule of reserpine, and so mere displacement of serotonin seems unlikely. That norepinephrine (arterenol) and/or histamine are often simultaneously liberated along with 5-HTA considerably complicates studies related to the effects of serotonin release.

The 5-HTA content of the gastrointestinal mucosa also varies considerably from species to species, and there appears to be no consistent relationship between the serotonin content of the intestine and the blood. Most of the total body serotonin is found in the gastrointestinal mucosa. The argentaffin cells probably represent the principal but not the only source of the serotonin which is formed outside the brain. A relationship between serotonin and intestine function has not been established, although recent in vitro studies by Bülbring and Lin strongly suggest that serotonin may sensitize mucosal stretch receptors for initiation of the peristaltic reflex, and thus 5-HTA may play a basic role in gastrointestinal motility.[31] Intravenous administration of small doses of serotonin[32] and serotonin precursor (5-HTP)[33] to man results in marked intestinal contractions, an effect possibly mediated by postganglionic cholinergic nerve fibers. The subject of serotonin and the gastrointestinal tract has been reviewed by Olson and Gray.[34]

The finding of serotonin and 5-hydroxytryptophan decarboxylase in the brain has excited considerable interest.[24,35] While it appears that serotonin produced peripherally does not enter the brain, it is generally agreed that serotonin can be synthesized from its precursor, 5-hydroxytryptophan, by cerebral tissue. In the dog and cat, the highest concentrations of serotonin are found in areas where autonomic integration occurs. The concept that serotonin may be of physiological importance in cerebral function is based on the finding of this compound in brain tissue; the hallucinogenic effects of certain antagonists and analogues of serotonin; the depressant effects of reserpine, which liberates serotonin from stores; the stimulatory effects of the amine oxidase inhibitor, iproniazid, which blocks serotonin degradation, and the pronounced central nervous system effects of exogenously administered 5-HTP.

Brodie and Shore have tentatively proposed the concept that serotonin performs a physiological function in the central nervous system by acting as a chemical mediator of parasympathetic impulses.[36] Much of the experimental evidence is contradictory, however, and there is still no direct proof that serotonin has a role in brain function. Evidence that 5-hydroxyindole metabolism may be altered in schizophrenia[37] is not supported by a recent report of a normal

blood serotonin and urinary 5-HIAA in this disease.[38] Abnormal mental function or striking emotional disorders have been observed only rarely in patients with carcinoidosis.

Serotonin is also found in small amounts in lung tissue. Comparison of the serotonin content of guinea pig and mouse lung is of interest.[39] The guinea pig lung contains small amounts of serotonin, and these animals are protected against anaphylaxis by antihistaminic drugs. The mouse, on the other hand, has relatively high levels of serotonin in the lung and is not protected against anaphylaxis by antihistamines. Whether or not anaphylactic reactions may in certain situations be mediated by serotonin remains unknown.

Whatever physiological role endogenous serotonin may have in the body, it is generally agreed that exogenous serotonin is an extremely potent smooth muscle constrictor. The guinea pig ileum, the pulmonary artery of dogs, the rat uterus, the clam heart are all so sensitive to serotonin in in vitro systems that they are used in methods of bioassay of serotonin. Erspamer believes that serotonin, by constricting afferent renal arterioles, acts as a regulator of glomerular filtration.[40] Small doses of serotonin in man result in bronchoconstriction and marked changes in respiration.[41] The actions of exogenous serotonin on smooth muscle are consistent with the cutaneous vascular changes, the bronchoconstriction, and the abnormal intestinal motility observed in patients with carcinoidosis. There is no direct evidence that serotonin can cause the peculiar endocardial fibrosis observed in these patients, although MacDonald has produced a similar lesion in subcutaneous tissue by repeatedly injecting small amounts of serotonin into the skin of rats.[42]

Investigations related to the formation, storage, release, and actions of serotonin have been so numerous and extensive that, in this paper, it has been possible only to comment briefly on some of the highlights. For further information on the recent review of these problems by Page[1] may be consulted.

Degradation of Serotonin

Free serotonin, in the presence of monoamine oxidase, rapidly undergoes oxidative deamination to form 5-HIAA.[6] That 5-hydroxyindoleacetaldehyde forms as an intermediate product in this oxidation has recently been demonstrated.[7] This compound is dehydrogenated so rapidly to 5-HIAA that it can be isolated only with difficulty during the oxidation of serotonin. Monoamine oxidase has been the subject of a recent review.[43] The enzyme is apparently capable of oxidizing tyramine and tryptamine as well as 5-HTA. Monoamine oxidase activity has been demonstrated in gastrointestinal mucosa, lung, kidney, brain, and liver.

That the 5-HTA present in blood passing from the right to the left side of the heart may be rapidly oxidized in the presence of lung monoamine oxidase may explain the valvular fibrosis found in the right but not the left side of the heart. This concept is supported by the finding of valvular heart lesions involving both sides of the heart in a patient with carcinoidosis and a patent foramen ovale,[44] although it was not shown that an actual shunting of blood from the right to the left side of the heart was present. Total serotonin content of pulmonary artery blood is not consistently greater than that of pulmonary venous blood in these patients. The amount of serotonin free in the plasma, on the other hand, is too small to measure accurately, and it is entirely possible that free rather than total blood serotonin may be responsible for the endocardial fibrosis.

Of considerable recent interest has been the demonstration of monoamine oxidase inhibition by iproniazid, a drug which has been used in the treatment of mental depression. Inhibition of monoamine oxidase by iproniazid has been demonstrated both in vitro and in vivo and by methods which demonstrate either accumulation of sero-

tonin in tissues or diminished production of 5-HIAA.[4,45] An in vivo test of the effectiveness of monoamine oxidase inhibitors in humans has been based on the finding that normally the recovery of orally administered serotonin as urinary 5-HIAA is practically complete.[45] Pretreatment with iproniazid or other effective monoamine oxidase inhibitors markedly depresses conversion of serotonin to 5-HIAA under these conditions.

The major final metabolic product of the 5-hydroxyindole pathway is 5-HIAA, which is present in large amounts in the urine of patients with carcinoidosis. Normal humans excrete 2-10 mg. of 5-HIAA daily. In carcinoidosis this value may rise to as much as 500-1,000 mg. A simple, highly specific screening test has been developed for determining increases of 5-hydroxyindole compounds in the urine.[46] This test is based upon the coupling of nitrosonaphthol with 5-hydroxyindole compounds to form a pink color. Except for carcinoidosis, marked increases in urinary 5-HIAA have not been reported. The significance of the slight but definite increases observed in patients with nontropical sprue[47] remains to be determined. Bananas contain significant amounts of serotonin,[48] and their ingestion results in elevation of urinary 5-HIAA.[49] As a result of 5-HTA liberation, administration of reserpine may be associated with a transient rise in urinary 5-HIAA.[50]

Diminished 5-HIAA excretion has been described in patients with renal insufficiency[51] and phenylketonuria.[20] Although a deficiency of serotonin has been postulated in the pathogenesis of hepatic coma,[52] the urinary excretion of 5-HIAA has been found to be essentially normal in patients with decompensated hepatic cirrhosis with and without encephalopathy.[15] Chlorpromazine and other phenothiazide derivatives suppress the color reaction used in the estimation of 5-HIAA, but these drugs do not cause an actual decrease in the amount of 5-HIAA excreted in the urine.[53] Lysergic acid diethylamide (L. S. D.) and other serotonin antagonists have no effect on 5-hydroxyindole metabolism and do not alter the amounts of 5-HIAA in the urine of experimental animals or patients with carcinoidosis.

Numerous studies of 5-hydroxyindole metabolism in man and experimental animals have suggested that mechanisms of serotonin degradation other than oxidative deamination exist. Hepatic conjugation of serotonin with the formation of serotonin-*o*-sulfate[54] and serotonin-*o*-glucuronide[55] has been described. The urinary excretion of 5-HIAA by rats given injections of serotonin or its precursor is increased in the presence of excesses of sodium orthoaminobenzoate, a compound which competitively inhibits glucuronide conjugation.[56] This would suggest that when less serotonin is conjugated more may be available for metabolism to 5-HIAA. Similarly, the greater than normal urinary excretion of 5-HIAA following intravenous administration of 5-HTP observed in patients with decompensated cirrhosis indirectly suggests that alternate mechanisms of 5-HTA degradation, such as conjugation, may be blocked in hepatic insufficiency. Other mechanisms of 5-HTA catabolism, including N^1 acetylation[57] and oxidation of serotonin in the presence of ceruloplasm in vitro to form a compound other than 5-HIAA,[58] have been described. Numerous authors have reported the formation of unidentified indoles following the administration of serotonin or its precursor to animals, and unknown indolic compounds have frequently been isolated chromatographically from the urine of patients with carcinoidosis. Thus, in spite of the rapid accumulation of knowledge in this field, understanding of the 5-hydroxyindole pathway of tryptophan metabolism remains incomplete.

Summary

Normally hydroxylation of tryptophan at the five position represents a quantitatively minor role in tryptophan metabolism. In malignant carcinoidosis, however, trypto-

phan hydroxylation with subsequent decarboxylation to form the biologically active amine, serotonin, becomes a major route of tryptophan metabolism.

The search for a physiological function of serotonin, together with intense interest in the clinical syndrome of carcinoidosis, in which excesses of a hormone are produced by tumor tissue, has led to extensive investigation of the 5-hydroxyindole pathway of tryptophan metabolism. Serotonin is apparently produced by argentaffin cells or other specialized cells and is transported in the blood by platelets. The mechanism of binding and release of serotonin is poorly understood. Although serotonin has been implicated in gastrointestinal, cerebral, and renal function, actual definition of the physiological role of serotonin in the body has not been accomplished.

Abnormalities of 5-hydroxyindole metabolism have been postulated in such diverse pathological states as sprue, hepatic coma, phenylketonuria, and mental disease. There is no direct evidence, however, that either serotonin or a deficiency of serotonin plays a significant role in the pathogenesis of any disease except carcinoidosis.

The conversion of serotonin to 5-hydroxyindoleacetic acid (5-HIAA) by oxidative deamination is the major route of serotonin catabolism, although there is increasing evidence that alternate mechanisms of serotonin degradation may be of importance.

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Books

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Neurotic Distortion of the Creative Process. By Lawrence S. Kubie, M.D. Price, $3. Pp. 149, with many illustrations. University of Kansas Press, Lawrence, Kan., 1958.

There is a legend which has almost universal acknowledgment and wide belief that artistic creation of many kinds has its genesis in neurosis. It is said that the artist has to keep his neurosis simmering in order to keep his creativity and productivity active. In this book, the three essays, which constitute the twenty-second series of the Porter Lectures of the University of Kansas, Kubie has prepared for the sensible layman or physician untrained as psychiatrist or psychoanalyst a clear and profound statement of the reasons for believing that such a philosophy about artists and creativity is worse than nonsense. It is a destructive denial of the truth. The truth is not only more palatable but much more hopeful.

Kubie's thesis is that the interplay of symbolic processes which comprise the instrument of man's creativity or of psychological illness must be under control to determine the form and fate of the creative process and check the neurotic process. By the introduction of very simple, but clear, diagrams and by his description of the preconscious Kubie has set forth stimulating ideas of remarkable clarity. The word conscious is clear enough to most of us. Even if we do not comprehend all that psychoanalysts since Freud have meant by unconscious we accept it as a subterranean pit in which the memory trace of much of our past is kept out of sight not only to avoid disturbing the neighbors but so we do not have to look at it ourselves. Nonetheless, it has the dynamic effect of a hidden flywheel and gyroscope combined, turning our actions and our lives along powerful but unseen lines of force. Between the conscious and the unconscious Kubie places ". . . an intermediate form of mentation to express at least by implication the neurosis of thought and feeling, those collateral and emotional references which cluster around the central core of meaning. Here every coded signal has many overlapping meanings; and every item of data from the world of experience has many coded representatives." This is the form of coded language which is essential for all creative thinking, whether in art or science. In technical jargon, this second type of symbolic process is called preconscious, and every moment of life the unconscious, the preconscious, and the conscious are in action concurrently, and well or sick, busy or quiet, everything we do, say, think, or feel is thought to be a kind of composite, a vector effect. The preconscious, where it dominates, gives freer swing to man's creativity and is not checkreined into immobility by an overactive conscience, nor is it deflected into futility or deranged into disease by a dominance of the unconscious. It is not possible by giving a few extracts to do credit to the distinguished exposition and convincing delineation of such constructs which to me anyhow are not only new but light up paths in an area which, if not totally devoid of maps and direction finders, at least has managed to cause many an unwary pilgrim to get lost. Anyone interested in accomplishment, productivity, and creativity as they are seen by one of the most perceptive and wise scholars in psychiatry and psychoanalysis must study this little book, whose shortness permits patient rereadings and detailed study.

Imagination and creativity, invention and discovery, are forces vital to the survival of man and of society. They are not evoked at will. They are fickle when courted most avidly but may come all unbidden. No autobiographical confession has made it clear how we can use the experience of another to catalyze our own inspiration. Where new ideas come from, and how, remain puzzles especially tantalizing because of the vital need to harness the great horsepower of creativity. John Livingston Lowes, in "The Road to Xanadu," described in wonderful detail the influences and sources from which arose the exquisite imagery and beauty of the "Ancient Mariner" and "Kubla Kahn." But no light fell on why the results were so stunning with Coleridge and so sterile with his compatriots who had the same general experience. Nor was it clear why the inspiration was lost without a trace and no recall by the intrusion of that classic example of the evil interrupter, the "person on

* Communications to this Department may be sent directly to Dr. William B. Bean, University Hospitals, State University of Iowa College of Medicine, Iowa City, or to the Chief Editor for transmittal to him.

business from Porlock." The method by which the stuff of dreams becomes the organ of the shaping spirit rather than the discontinuous flotsam and jetsam of existence, Coleridge himself said, lay in "the streamy nature of association, which thinking curbs and rudders."

Ghiselin, in his collection of biographical and autobiographical analyses of "The Creative Process," has as many versions of how inspiration comes as he has examples of it. The circumstances are clear enough. But the why, intangible, evading our most intense efforts, remains unknown. To this how and why Kubie has addressed himself in his stimulating book. While the primal stimulus to creativity is clear enough, Kubie does not disclose what sets it going. But he does demonstrate convincingly that the creative process is strangled, not stimulated, by neurosis.

WILLLIAM B. BEAN, M.D.

Atlas intracardialer Druckkurven (Atlas of Intracardiac Pressure Curves; Atlas de Curvas Tensionales Intracardiacas). By Prof. Dr. Otto Bayer and Dr. Hans Helmut Wolter. English translation by G. R. Graham, M.D., London; Spanish translation by E. Low-Maus, M.D., Barcelona. Price, $16.20. Pp. 185, with 97 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N, Germany, 1959.

This book is unique, in a way, because it presents its topic in the German, English, and Spanish languages. Dr. Cournand, who wrote an introduction to the book, is of the opinion that medical students, practitioners, specialists in cardiology and even physiologists will be pleased to find in it a host of information regarding intracardiac pressures. Cardiac catheterization is a generally accepted and rather young diagnostic tool and is practiced in many hospitals throughout the world. A presentation of the characteristics of different pressures organized in a book form is, therefore, rather overdue.

Following an introduction, a description of the technique and the apparatus and some theoretical considerations concerning pressure transmission through a fluid column in a semi-rigid cardiac catheter and normal pressure curves from the ventricular chambers, the arteries, and the venous chambers are presented. Simultaneous electrocardiograms and phonocardiograms were taken with the pressure curves. The pressure curves are analyzed and correlated with hemodynamic events. The quality of the curves in the text and in the plates is excellent and indicates a superior technique of the authors. The authors firmly believe that the pulmonary "wedge" pressure curves reflect pulmonary venous and left atrial pressure events if proper techniques are used. This is not the view of all cardiac physiologists, although it is recognized by all, that under certain circumstances "wedge" pressure will reflect left atrial pressure changes. The authors admit the pulmonary "wedge" pressure is subject to more artifacts than any other pressure curves and it is often necessary to obtain wedge tracings from several branches or even different parts of the lung.

Distortion of the pressure curves by inadequate recording by the apparatus and artifacts from other sources follow the presentation of the normal curves.

In the second section of the book, abnormal pressure curves are discussed. The changes of the curves due to arrhythmias of different origin, further to premature systoles, paroxysmal tachycardias, and bundle-branch blocks are presented. Following that, characteristic pressure changes in valvular stenosis and insufficiency are discussed. No mention is made of the different attempts to estimate the predominant lesion from the "Y" descents of the atrial pressure curve. The degree of mitral and tricuspid insufficiency is estimated mainly from the systolic elevation (CV-wave) of the atrial pressure curve.

Pressure changes in intracardiac shunts is the next topic discussed. The significance of ventricular and atrial septal defects is evaluated by comparing ventricular or atrial pressure tracings from the left and right chambers. It is the merit of the authors to point the significance of the height of the V-wave in the left atrial pressure tracing as an aid in estimating the significance of an interatrial shunt.

In the final chapter, pressure changes in constrictive pericarditis and diastolic failure of the right ventricle are discussed. The last part of the book contains illustrations pertaining to the discussed subjects.

The book is an excellent guide for the student of cardiac pressure tracings, whether for general information or for the use in the cardiac catheterization laboratory. A few typographical errors may be corrected in a second edition: for instance, on page 119, the inter-

pretation of the pressure curves "A" to "D" erroneously says "right to left" instead of "left to right" interatrial shunt. The printing of the book is of excellent quality.

PAUL KEZDI, M.D.

Klinische Enzymologie: Die Fermente in der Pathogenese, Diagnostik und Therapie. By Rudolf Abderhalden, M.D. (Privat-Dozent). Price, $11.40. Pp. 398, with 34 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N, Germany, 1958.

The author presents a survey of the rapidly growing field of clinical application of enzymology and succeeds well in his endeavor to "stimulate interest in what is probably the most fascinating field of research in modern medicine." In the introductory chapter, the basic precepts of enzymology are presented for the nonspecialist in succinct, but clear, fashion. This leads into the main part of the book, a thorough discussion of about thirty mammalian enzymes, which have been connected in some way with clinical findings or therapy. For each enzyme, the reaction catalyzed is presented, the occurrence and physiological properties are summarized, and pertinent effects of drugs and methods of assay are described briefly. The literature dealing with the association of the enzyme and disease states is discussed in detail and critically assessed. The value of determining a quantitative enzymatic pattern as a diagnostic tool is pointed out. It is regrettable that such enzymes as monoamino-oxidase and xanthine oxidase, which figure prominently in modern research of brain metabolism and of cancer, should not have been dealt with.

The next section of the book deals with another recently developing field, the inborn errors of metabolism and their correlation with specific enzymes and enzyme systems, that is to say, the relationship between enzymes and hereditary disease. The final section of the book deals with therapeutic application of enzymes, encompassing mainly proteinases, thrombin, and hyaluronidase. Within the framework of the book, some antivitamins and other drugs, especially azetolamide, received excessive attention, perhaps to the detriment of other compounds known to affect key enzyme systems. This is also the case with the so-called "Abwehr-fermente" (defense enzymes) postulated by E. Abderhalden and his school.

Some statements expressed are open to question, such as the classification of enzymes into desmolases and hydrolases, the assertion that all enzymes necessarily contain cofactors or activators, or the distinction drawn between bacteriophage and virus, which generally are no longer accepted. Some of the findings discussed are not as clear-cut as here presented; however, on the whole, the author presents a balanced view of controversial reports in the literature.

The book contains an up-to-date bibliography of almost forty pages, dealing mainly with clinical aspects and therapeutic application of enzymes, which is a valuable source for reference and a good starting point for readers interested in research.

In the prefatory chapter, the author modifies a saying of Willstatter: "Life is the regulated interrelationship of enzymatic processes," adapting it to read: "Disease is a disturbance of the harmonious interaction of enzymes."

The book is well printed, containing a number of clear graphs and tables. It constitutes a valuable addition to the library of medical research and should be of interest to all investigators in this field.

RAINER FRIED, PH.D.

The Pneumoconiosis Problem, with Emphasis on the Role of the Radiologist. By Eugene P. Pendergrass, M.D. Price, $6.75. Pp. 146, with 53 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1959.

Admitting that he has not written a complete treatise on pneumoconiosis, Dr. Pendergrass has collected his thoughts on certain aspects of the problem which have interested him. On these topics, he gives us much valuable information. As a radiologist, his knowledge and interest have been unique. The roentgenologic manifestations of pneumoconiosis are dealt with in length and detail. The difficulties and deficiencies in radiographic diagnosis are discussed, and classifications are advanced and criticized. Problems of high clinical import, such as the relationship between pneumoconiosis and other lung disease—notably, tuberculosis, the assessing of disability, the correlation of x-ray appearance with lung function, and the modifications in the radiograph during the life history of the disease, are also well covered. No mention, however, is made of the lung lines described by British writers as occurring from lymphatic blockage in pneumoconiosis.

Pneumoconiosis is a problem of importance, but we can not agree to the statement, "There is no part of radiology in which there is a greater opportunity for contributing real service to the health of the community and of the nation." Dr. Pendergrass' experience is broad, encompassing observations of several hundred workers for as long as twenty years. Several questions are raised: How early can the diagnosis be made? Is x-ray filming the most valuable detector? Can x-ray help in evaluating disablement? Perhaps these answers will only come from his attempt to awaken physicians, and radiologists in particular, to an interest in these problems.

H. W. FISCHER

Roentgen Diagnosis of Abdominal Tumors in Childhood. By Charles M. Nice Jr., M.D., Ph.D.; Alexander R. Margulis, M.D., and Leo G. Rigler, M.D. Price, $4. Pp. 73, with 52 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

The thesis is simple and not new. A mass in the child's abdomen can be accurately located by radiologic examination. Conventional, plain film study is used first. Barium gastrointestinal study and enemas, excretory and retrograde urography, and intravenous cholangiography follow if needed. These examinations, affording observations of the size of the mass, its contour, variation with change in position, presence of calcification, or other internal characteristics, can then be correlated with the clinical and laboratory findings and the sex and age of the patient to give an accurate diagnosis in the light of statistical probability. The more complicated less readily available radiographic techniques, such as presacral gas inflation and aortography, are only rarely needed. Simple and as obviously worthy as this thesis of Drs. Nice, Margulis, and Rigler may be, it needs reiteration. They have written a book limited in scope, yet their coverage of their subject is complete. Necessary anatomical information is given briefly. A reasonable organization is made into masses in the region of the liver, other intraperitoneal masses, renal and adrenal masses, and other extraperitoneal masses. Each type of neoplasm is then described thoroughly as to its roentgen characteristics. Those already aware of the value of the radiologic techniques will find great value in the systematic consideration of all pathological types of abdominal tumors of this age group.

H. W. FISCHER

Cold Injury. By M. Irene Ferrer, M.D. Price, $5.95. Pp. 341, with many illustrations. The Josiah Macy, Jr., Foundation, 16 W. 46th St., New York 36, 1958.

The bleak northland of Eskimos and polar bears, of the aurora borealis, and of infinite desolate waste has become of supreme importance as a none too firm barrier between ourselves and the Russians. Since the overland dash of Perry, it has been conquered by flying over it and going under it in a submarine, but the real problems of how man lives and how the Eskimo manages, despite the fact that they have had intensive study from various points of view, have not yet yielded a body of scientific knowledge which enables those who make plans to devise a program of exercise, food, water, clothing, and shelter which will make probable, much less guarantee, successful performance when man is removed from his temperate environment and thrust into the Arctic, not only to survive but to achieve his mission as a soldier on the ground or a flier. This book by the experts in this field sums up much of the knowledge available and in so doing points out with stringent directness the conspicuous defects in our knowledge of our many essential points in Arctic lore. Part of the trouble resides not so much in the absence of data but in the failure of a complete synthesis of those which are available and a systematic program whereby they might be put into effective use. One senses the same frustration which was all too apparent early in World War II, when it was found that many machines and much equipment had been designed without sufficient regard for the human element in the soldier. Indeed, it was the human element that was the limiting factor in tanks, in submarines, in planes, and, for that matter, in close combat by infantry troops or attacks by commandos.

In addition to the interest that a cold environment has for a biologist with wide interests in human biology and adaptation, the use of hypothermia to induce anesthesia for heart operations and others and the possible employment of anesthesia in space travels as well as in the treatment of a number of diseases where, theoretically, reducing or suspending the body metabolism might have useful effects are dealt with in several sessions of this con-

ference. The tremendous importance of motivation as it refers to fitness in performance of soldiers, the inability of our present techniques to disclose all of the means of education and native wit which enable the Eskimo to adapt and perform so well, the intense difficulty of obtaining precise data in the field, and the difficulty of translating laboratory studies on man to field conditions are illustrated in many places throughout the book.

The editing seems to be a little sharper in this book than in some, though it must be embarrassing for some of the participants in the conference to have their casual and not always clear thoughts recorded in such an informal way for posterity. The editorial insertion of certain items which were not remembered at the time of the conference but which bear on the problem at hand is a welcome improvement over some of the previous conferences. Anyone interested in human adaptation to environment and anyone with an interest in the physiology of cold and many of the biological problems of hibernation, cold acclimatization, and trauma from cold will find this book interesting and at the same time frustrating, as may, perhaps, be illustrated by the final few pages which deal with certain paradoxes and discrepancies in our understanding of cold as illustrated by the bizarre effects of cold in a hypnotized subject.

WILLIAM B. BEAN, M.D.

Amino Acids and Peptides with Antimetabolic Activity. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Cecilia M. O'Connor, B.Sc. Price, $8.75. Pp. 286, with 28 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1958.

This volume records the proceedings of a Ciba Foundation international symposium. The amino acids and peptides with biologic activity were under surveillance, and the discussions dealt especially with those having antimetabolic and cytotoxic properties. Twenty-nine participants, under the chairmanship of Prof. F. Bergel (Chester Beatty Research Institute, London), took part in either the formal presentations or the discussions.

Much attention was directed to the antibiotics. Particularly, this book will interest persons dealing with or interested in the chemotherapy of neoplastic diseases. While the presentations often dwelled upon the highly technical aspects of biochemistry, the discussions were broadened; then too, an array of related material was encompassed, and the book thus tends to balance toward biology and the clinical sciences.

The tables and illustrations are liberal and lucid; the print and format are good. The documenting references are from a broad literature. The book will find a useful place in a hospital or laboratory library.

ROBERT C. HICKEY, M.D.

The Doctor Business. By Richard Carter. Price, $4. Pp. 283, with no illustrations. Doubleday & Company, Inc., Garden City, N. Y., 1958.

We all have watched the floods of anger and annoyance raising the water in the great reservoir of ill will against physicians, against "organized medicine," and against the American Medical Association. The dams of restraint have burst, and this book has come flooding out full of passion and outrage. Though the author is no beatnik throwing in the towel of life, he has carried his privilege of weeping at the wailing wall beyond the call of duty. He floats off in an ocean of tears, as Alice in Wonderland did, beset by hordes of imaginary rodents. Most of the criticisms about the medical profession are true in the case of some doctors. The good physician deplores this as bitterly as Carter does. But medicine has no monopoly on evil. In spite of what one would judge from Carter's book, physicians are much oftener than not compassionate and hard working and are not money-grabbers. The great constructive work of the American Medical Association, in raising the level of medical practice, in making licensing adhere to a standard to which the just and honest could repair, in improving medical education, in increasing the efficiency of hospitals, and in making many other constructive contributions is lost in the torrent of complaint. Certainly there are ghost surgeons, dollar-snatchers, connivers for insurance, fee-splitters, those who do unnecessary surgery for the money in it. The scoundrel and the quack have always existed. Carter's book will not reduce either their number or their evil. Those who have had intimate experience with certain kinds of group medicine, such as in the Army or the Navy, will know that it may achieve high standards of excellence but that built-in odds against this being achieved regularly are higher in any complex but rigid organization than in the prac-

tice of medicine in an open social system. Only exceptionally have hospitals under government auspices risen to the level of excellence of the great group clinics in the country, though some are superb.

The lack of balance in this terrible-tempered book does not veto or deny that Carter has put his finger upon many a sore spot. These need to be known by the public as well as by physicians who know them already. Certainly, it would be fine if someone could devise a method of educating the public in a sound knowledge of medicine. The layman might not be so easily bewildered by the Madison Avenue techniques of more flagrant advertisers. It would reduce the mock heroics of medicine, which makes each drug a miracle and each operation worthy of a Nobel prize. It would indoctrinate the patient with knowledge of the limitations of medicine and of physicians, as well as their capabilities. For all its miracles and wonders, which are many, medicine and science have not yet staved off individual death. Nor will they.

This book is another in the paranoid series. Its thesis is that by virtue of being born a person is owed health and medical care as a birthright. Insurance cannot guarantee Utopia. The ideas of working for what one gets, of not depending on government or other handout, of personal endeavor rather than something for nothing have declined notably within a generation in our country. Replacing them by womb-to-tomb security, the will-o-the-wisp of the sputnik-beatnik will lead to a slowly necrotizing jelly of inertia into which our civilization will settle and vanish. Faults in medicine and among physicians there are aplenty, but we should keep in mind Hippocrates' warning, "Don't make the treatment worse than the disease."

Despite its one-sidedness, this book is of challenging importance for all physicians, who must be aware that one of the reasons for increasing distrust, skepticism, malpractice suits on flimsy evidence, and similar phenomena resides in lack of understanding and lack of compassion, which have led to many of the evils upon which the physician may go astray, the patient be harmed, and the public lose confidence. At the same time, tempering criticism with justice should not be forgotten by even the most violent pamphleteer, lest he be consumed in his own heat and the ashes of his efforts blow away, obscuring vision but not generating useful steam.

WILLIAM B. BEAN, M.D.

Differentialdiagnose innerer Krankheiten. By Prof. Dr. Robert Hegglin, Privatdozent an der Universität Zürich, Chefarzt der medizinischen Klinik, des Kantonsspitals St. Gallen. Price, $18.85. Pp. 819, with 517 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N, Germany, 1959.

Dr. Hegglin's differential diagnosis of diseases of internal medicine has gained wide acclaim in Europe. This is the sixth revised and augmented German edition since 1952. The book is also available in Italian and Spanish. A chapter on paralyses of the muscles of voluntary movement has been added in the present edition.

The foreword is preceded by a word by Pascal which is repeated here because it defines the scope of the book: "Puis' quon ne peut etre universel et savoir tout ce qui peut se savoir sur tout, il faut savoir peut de tout. Car il est bien plus beau de savoir quelque chose de tout que de savoir tout d'une chose." Within this scope, the book gives an astoundingly complete picture of differential diagnostic problems in internal medicine. The correlation of the clinical findings with the underlying physiologic mechanism is stressed. In each chapter, the problems of differential diagnosis are discussed as they arise in the presence of an important symptom or sign. In my opinion, this approach has the drawback that different aspects of the same disease are discussed in different chapters. For example, the main reference to primary aldosteronism is found in the discussion of hypokalemia and its effect on the myocardium. It is again briefly mentioned under hypertension. Different facets of fungus infections are found under febrile illnesses, pulmonary infiltrates, and pain in the extremities.

To write a differential diagnosis of internal medicine within a relatively limited space, there has to be a compromise. As pointed out by the author in his foreword, some topics are treated in a sketchy manner, while others are discussed thoroughly. However, the lack of information in certain areas could be supplemented by a more extensive bibliography. For example, on page 205 we find the following paragraph on pulmonary diffusion defects: "It is still unsettled if pulmonary diffusion defects in the presence of altered alveolar walls

(alveolo-capillary block of the Americans, pneumonose Brauer), may result in decreased gas exchange, i. e., hypoxia and hypercapnia." According to Rossier, pulmonary diffusion defects are predominantly due to a shortened contact time following the loss of functioning capillaries by fifty per cent or more. Such a representation seems biased and moreover based on a minority opinion and does not consider the work of a score of other investigators who came to different conclusions. On page 293, in a discussion of primary pulmonary sclerosis, no mention is made of the concept of primary pulmonary hypertension.

Some of the statements could be more precisely formulated. For instance, on page 305 it is stated that in pulmonary stenosis "the intracardiac pressures are altered in a typical manner. The pressure in the atrium is found to be about 10 mm. and within normal limits." There is no mention whether this value of 10 mm. refers to a mean pressure or maximal pressure and whether is represents millimeters of water or mercury.

The book is written in a very readable German. It is meant primarily for the medical student and was written with the intent to convey an approach to the art of differential diagnosis. Because of its briefness in some areas, the student could benefit from a more critically selected bibliography with reference to comprehensive reviews and original articles and with less emphasis on textbook references. This would also be appreciated by the foreign reader, who, as a rule, has far better access to periodicals than foreign language textbooks.

HANS U. WESSEL, M.D.

Ideals in Medicine (A Christian Approach to Medical Practice). By Vincent Edmunds, M.D., M.R.C.P., and C. Gordon Scorer, M.B.E., M.D., F.R.C.S. Price, $3. Pp. 192, with no illustrations. The Christian Medical Society, 127 S. Wacker Dr., Chicago 6, 1958.

Most physicians are notably reluctant to deal with matters having any taint of philosophy, morals, manners, or ethics. Such are considered to be beneath their dignity or outside what they believe is their proper scope of activity. Younger members of the profession may feel this lack particularly. They have a hard time finding where to turn for a discussion of beliefs upon which they should form opinions in order that their practice may be more than a mechanical routine of reflex responses. Naturally, it is impossible for any book to answer all the questions that might come up in any person's search for a philosophy of life and medical practice. A British physician and a British surgeon with several colleagues have faced such problems in "Ideals in Medicine."

With the world divided into two hostile camps, it is well for physicians as well as scientists in the Western world to remember that whenever the state has supremacy over the individual, medicine as we know it withers. Some of the problems which confront us physicians in dealing with patients exist in obvious conflict one with another because we have divided loyalties. In the current state of medicine these are more acute than ever. We have our obligation to the patient but also obligations to society, to the state, and to our own ethical and moral beliefs. These in turn are determined by religious beliefs or by the "attitudinal sets" of the mechanistically minded who consider themselves to be complex replicating machines. Regardless of personal beliefs, in Western society medicine cannot be detached from or exist out of context with the basic Christian beliefs. Leaving out matters of doctrine or sect, the duty of the Christian to his neighbor or the Christian physician to his patient has its best expression in the "Sermon on the Mount" and the "Golden Rule." In these few words we have summed up the physician's care for the patient, which is so vital to his cure.

An example of what happens when medicine loses the stabilizing and elevating force of Christian ethics is seen in the degradation of medicine in Nazi Germany before and during World War II. While there had been some clues to this in the profound disregard of the patient which Brown, Cannon and Zinsser noted in some German clinics, the patient was not regularly medical fodder for the department head or chief of clinic. Nonetheless, in Germany when doctors of infamy began their "experiments" on human subjects, and when the political pogrom aimed at annihilating the Jews had the afterthought of finding some utilitarian byproduct of their death and destruction, their medical profession sank to its lowest state in all recorded history.

There are many helpful chapters in this book which gives undergraduate student and the fledgling physician, as well as those who have had much experience, in practice an opportunity for some detailed introspection. Every physician must make up his mind about standards. The physician without a sound philosophy will be of little help for the sick, the suffering, or the dying. This volume is a useful primer which includes the major problems of morals and ethics in medicine seen in the context of the Christian heritage of Western man.

WILLIAM B. BEAN, M.D.

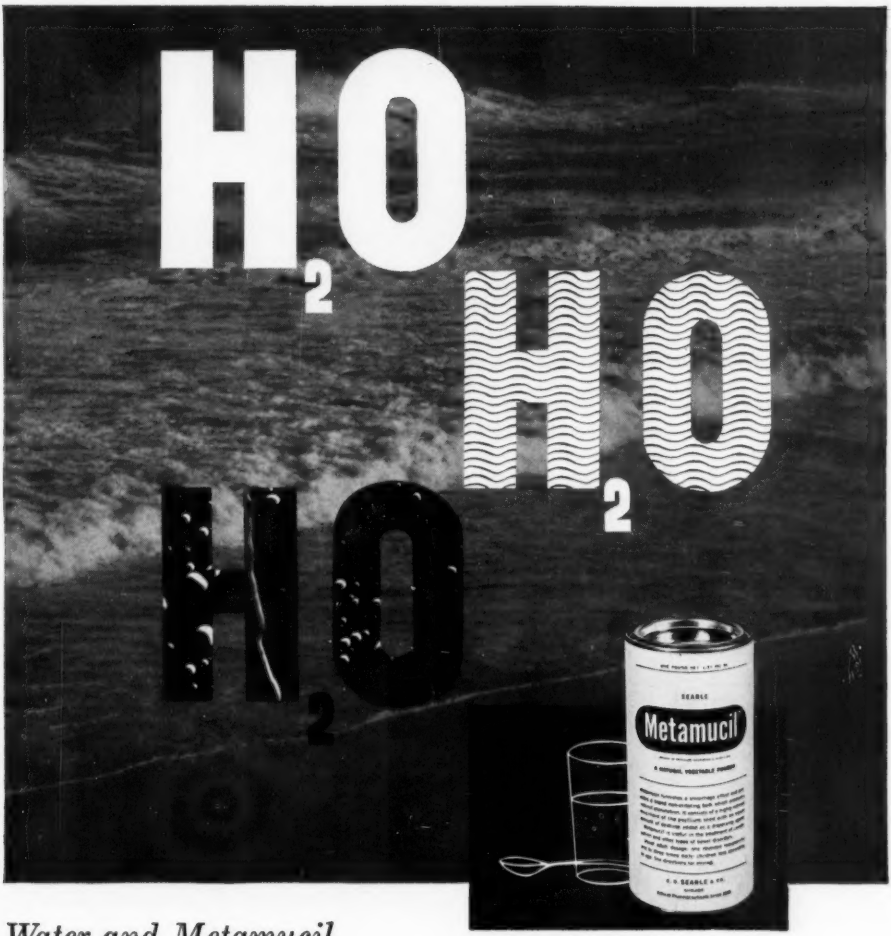
News and Comment

ANNOUNCEMENTS

Urology Award.—The American Urological Association offers an annual award of $1,000 (first prize of $500, second prize $300, and third prize $200) for essays on the result of some clinical or laboratory research in urology. Competition is limited to urologists who have been graduated not more than 10 years and to hospital interns and residents doing research work in urology.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Palmer House, Chicago, May 16-19, 1960.

For full particulars, write the Executive Secretary, William P. Didusch, 1120 N. Charles St., Baltimore. Essays must be in his hands before Dec. 1, 1959.



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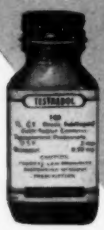

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Pylorospasm or cardiospasm	11	2
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Miscellaneous	7	29
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Clinical Results *Excellent*	445	150
Fair	56	—
Failure	68	6

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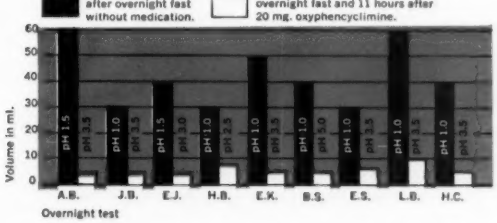

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1. Bellet, S.: Finkelstein, D., and Gilmore, H.: A.M.A. Archives Int. Med. 100:750, 1957.
2. Bellet, S.: Amer. Heart J. 56:479, 1958.

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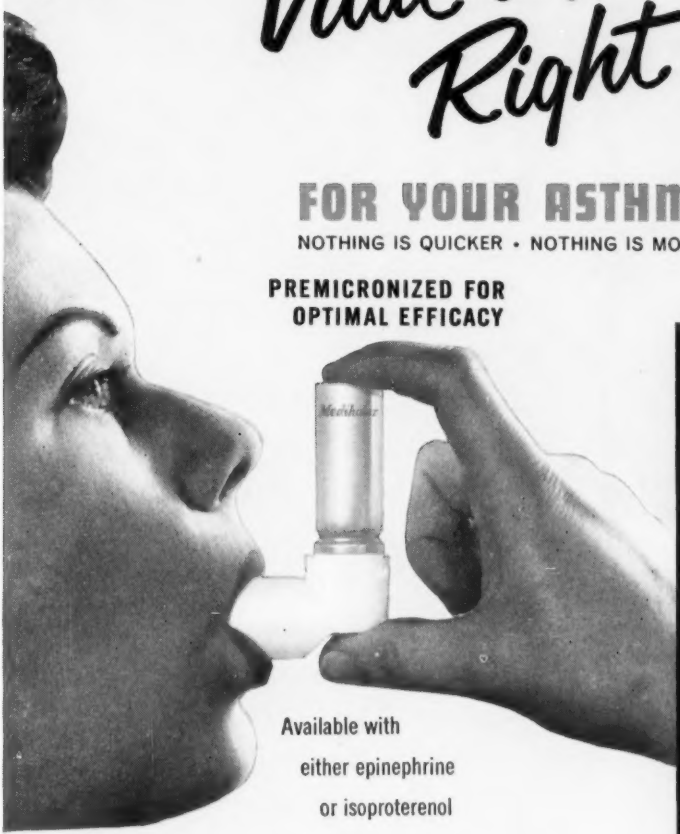

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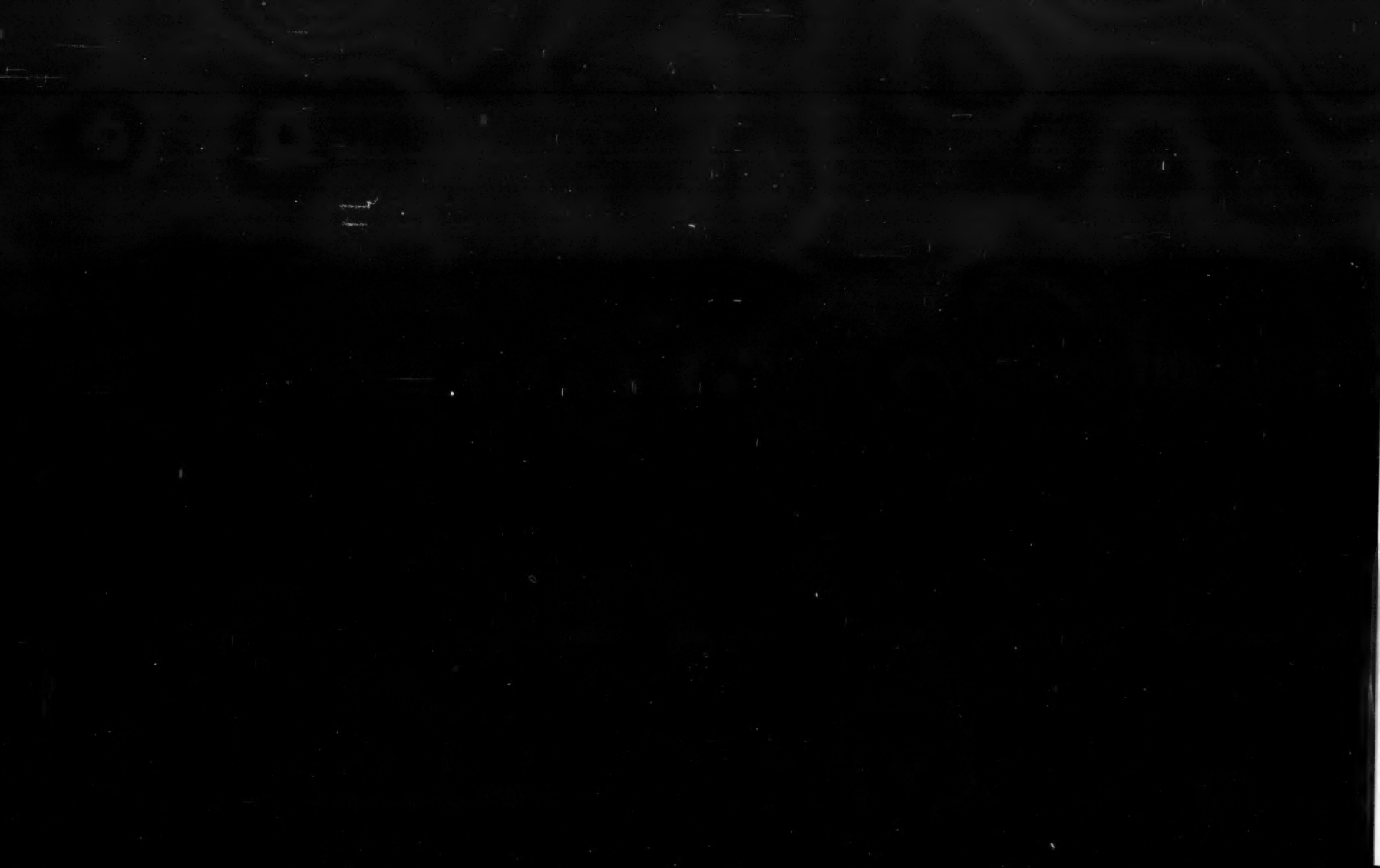
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